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THE BLISTER HYPOTHESIS AND THE OROGENIC CYCLE

By C. W. WOLFE*

Introduction. One of the outstanding problems confronting geologists today is the origin of continents and ocean basins, phenomena which are too frequently taken for granted. It is unreasonable to suppose that an originally liquid earth would have been divided on the surface into sialic and simatic sectors. The Pacific basin, in particular, is apparently unique in character, and the obvious conclusion is that this basin, at least, passed through a peculiar and probably cataclysmic stage during which the originally ubiquitous sialic layer was ejected from the region.

This idea has long been known. George Darwin suggested that, since the moon's tidal effect produces a retardation of the earth's rotational velocity, which is accompanied by a retreat of the moon from the earth in order to maintain the angular momentum of the rotating earth-moon system, a reversal in time brings the moon ever nearer the earth, until, at last, it is a part of the earth, protruding from that body as a pronounced bulge. If we imagine that the earth passed through a liquid phase, during which density stratification of the entire planet occurred, we can assume that beneath a surface layer, perhaps 30 km. thick, of the composition of granite an equally thick layer was formed of the composition of diorite which, in turn, was subtended by a layer of the general composition of gabbro to peridotite, probably extending to a depth of at least 600 km. To produce a body of the mass of the moon from the approximate present area of the Pacific basin would require removal of materials from the earth to a depth of about 132 km. The specific gravity of the moon is about 3.45, and this density is consonant with the Pacific origin to the depth already postulated.

* Department of Geology, Boston University, Boston, Mass. This paper, illustrated with lantern slides, was presented at the meeting of the Section on March 7, 1949.

It is likely that before the separation of the moon from the earth a universal ocean covered the thin crust then in existence. The ejection of the moon created the ocean basin in the Pacific area, and, for the first time, dry land appeared, erosion began, and sedimentation was possible. Thus, the Archean sedimentation began. During the Paleozoic era, the moon was still relatively close to the earth, and, since the height of tides is, approximately, inversely proportional to the distance of the moon, at that time they were perhaps ten to twenty times their modern height. It was probably this close proximity of the moon which was most responsible for the development of the well-known, widespread, homogenous, epicontinental marine deposits of the Paleozoic era.

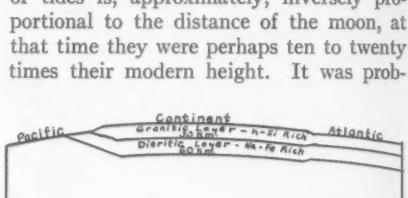

FIGURE 1. Density stratification of outer earth

It is important to realize that this suggestion for the origin of the Pacific basin is not germane to the blister hypothesis that follows. It is given here simply because, while the Blister Hypothesis can adequately explain other ocean basins and also the continents, only some cataclysmic act, such as the moon ejection, can explain the Pacific basin with its magnesium-calcium rich simatic floor. FIGURE 1 indicates the author's view of the distribution of lithologic types in a representative section of the earth today.

A second problem confronting geologists is the origin of large crustal movements, some essentially vertical, some essentially tangential. This is the problem of plateau formation, of mountain building, and of sinking lands. Although no relation between the origins of these various phenomena need exist, their general association in time and space seems to point strongly toward a common origin for all crustal movements, each perhaps representing a momentary picture in an overall cycle of development. That this might well have been the case will be demonstrated in the following treatment of the Blister Hypothesis.

No adequate theory of earth movements is possible without a clear understanding of the various types of mountains: the erosional, the domal, the fault block, and the compressional mountains. The explanation is no more difficult for one type than for another, although the compressional mountains have received the greatest share of attention from geologists in general. Probably, this is because of the tremendous circumferential shortening which is suggested for such regions as the Alps and the Himalayas. The author believes this shortening to be much exaggerated, and an explanation for the apparent shortening of the crust is readily to be found.

Coupled with the problem of mountain origins is the problem of the constant association of post-Cambrian regional metamorphism and ore emplacement with zones of compressional mountains. These problems move hand-in-hand with the problems concerning the distinctive character of pre-, syn-, and post-tectonic igneous intrusions. Since these, too, in post-Cambrian time, are associated with zones of compressional mountains, it seems entirely reasonable that all these phenomena are interrelated and dependent on the same major cause.

The fact that regions of folded mountains are restricted to definite belts with definite patterns is important to the problem, as is, also, the fact that mountain building is not a continuous process in one region, but is interrupted by what are, apparently, much longer periods of quiescence. In certain sections, however, such as California, quiescence is a relatively rare phenomenon; and this, too, needs explanation.

It is impossible to treat here the objections which have made unacceptable the other hypotheses of mountain building. The fact that no single present hypothesis is accepted by even a sizable minority of geologists is sufficient excuse to warrant the development of another. Perhaps the Blister Hypothesis, as it is presented here, will prove even less acceptable. But even by the rejection of impossibilities progress is made, and thus the hypothesis is here given.

Formation of Blister. A Blister, by definition, is an expanded subcrustal sector of the outer shell of the earth. It is assumed, here, that this expanded region lies in a zone not less than 15 km. and not more than 600 km. below the surface. The physical state of this expanded sector may be either expanded crystalline, glassy, expanded glassy, or, in the final stages, liquid. It is supposed that a Blister may pass through all of these stages before its final collapse and disappearance, but there may be periodic reversals in the trend of development due to the escape of heat, usually in the form of magma.

The cause of the expansion in the Blister is the release of energy associated with radioactivity. Unfortunately for the hypothesis, the amount of radioactivity in depth is not known, although there appears to be enough to make the entire earth liquid if continued through to the center in the same degree of concentration as at the surface. The author believes that the ease with which the Blister Hypothesis explains the various, previously mentioned problems is evidence that radioactivity, to a depth of 600 km., is adequate for the requirements of the hypothesis, since no other adequate energy source can be envisioned.

It is assumed that radioactive elements are not homogeneously disseminated throughout this region. In fact, it could

hardly be expected. Thus, it can be imagined that, in certain relatively localized areas, pockets of trapped energy would develop where the loss of heat by conduction and radiation is not so great as the heat produced by radioactive decay. Some heat is, of course, being conducted away at all times. But, if heat gain exceeds heat loss, the rock in that area must necessarily become warmer, expand, and form the nucleus of a Blister. The rate of heat loss would depend primarily upon the physical nature of the rocks wherein the heat is being generated. In surface rocks, with their high crystallinity, their fractures,

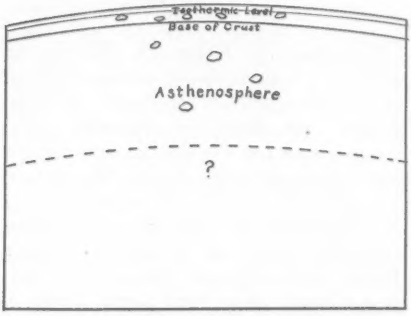

FIGURE 2. Pocket blister phase

and their connate and meteoric water content, heat loss exceeds, or is commensurate with, the heat gained from conduction from below, and from radioactivity in the zone itself. But, below a depth of, approximately, 15–20 km., which is here called the *isothermic level*, the physical state of the rocks is such that the rate of heat generation, though probably about the same as in the rocks above the isothermic level, exceeds the rate of conduction away. Thus, the rocks become progressively warmer. The first stage in the development of a Blister, then, is the development of *pocket blisters* in random positions beneath the isothermic level, but above the 600 km. depth. Some would develop in the crystalline, strong crust, and others would develop down in the weak asthenosphere (FIGURE 2).

Gradually, the Pocket Blister volumes would increase, their boundaries would extend, and coalescence would take place. This stage is known as the *Master Blister* phase (FIGURE 3). It is important to realize that the continued growth of the Blister can be only lateral or in depth, for, above the isothermic level, heat loss will always be commensurate with heat gain, and there will be no pronounced expansion through a change in the physical state of its materials.

It is probable that the proportions of the Blister would approximate a thick,

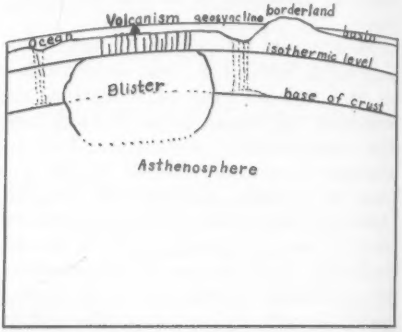

FIGURE 3. MASTER BLISTER. Development of geosynclines, borderlands, and basins volcanism above blister with lengthening of crust.

doubly convex, circular lens. The diameter of the lens parallel to the earth's surface would probably be at least 500 km. and might readily be thousands of kilometers, perhaps of continental or oceanic proportions. The vertical thickness would almost certainly reach 100 km. and might easily be more. If we place a conservative estimate of 10 per cent upon the cubic coefficient expansion of rock from the crystalline to the less ordered states, it is immediately apparent that a Blister with a thickness of 100 km. would be manifested at the surface of the earth by a rise of 10 km., which is well within known figures of vertical movements of the crust. An even larger figure is certainly possible. Thus, considerable epeirogenic uplift can be readily explained.

Development of Crust Above Blister. A radial extension of the crust, which is caused by the expansion of the Blister, is accompanied by a circumferential lengthening at the surface. The magnitude, in any one direction, of this lengthening (ΔL) may be expressed by the formula $\Delta L = 2\pi\Delta R \cdot \frac{w}{40{,}000}$, where R is the difference in radius caused by the expansion; w is the width of the Blister parallel to the surface of the earth; and $\frac{w}{40{,}000}$ is that fraction of the entire earth's circumference occupied by the Blister. If, for example, we assume a radial expansion of 14 km. for a Blister whose width is 2000 km., the equation reads, by substitution, $\Delta L = 2 \cdot \frac{22}{7} \cdot 14 \cdot \frac{2{,}000}{40{,}000} =$ 4.4 km.

Surface rocks above the isothermic level are extremely likely to rupture when subjected to tension. When a Blister develops beneath the crust, and its increase in volume is accompanied by a radial expansion outward, the only possible adjustment to the circumferential lengthening demanded by the equation is through fissuring. The first fissures to develop would reach down to the roof of the blister, where the materials are in either a glassy or liquid state. The release of pressure in the former case would be adequate to cause a transformation to the liquid state. Consequently, in either case, magma would rise toward or to the surface, from the Blister area. The chemical nature of that magma would be key information as to the depth from which the magma rose. The loss of magma produces two important results. First, there is the decrease in Blister volume produced bythe loss of magma; and, second, there is the loss in Blister energy produced by the expansion and escape of the Blister materials. Each of these means loss of volume, and this is manifested by a radial shrinkage and pulling in of the Blister roof.

As the roof tends to collapse, two important changes which have transpired make a return to the original position impossible. The magma which was intruded into the fissures above the Blister might well tend to solidify in the fissures, thus increasing the length of the crust in that sector by an amount equal to the original circumferential lengthening. At the same time, the intruded and extruded material effectively decreases the thickness of the Blister, and the collapsing roof must settle down to a lower position than it had formerly, the total amount of the shrinkage being perhaps 125 per cent of the original radial extension. Returning to the example given earlier, where a circumferential lengthening of 4.4 km. was suggested, we find that a shrinkage of the radius to the roof of the blister of 1.25×14 km. means a circumferential shortening of 5.5 km. This circumferential shrinkage must be manifested by folding or/and overthrusting.

It is unlikely that a total collapse would take place as simply as this. It is rather to be imagined that the movement above the Blister will be comprised of a series of pulsations of expansions and collapses. In depth, the Blister grows wider and deeper constantly, as the roof passes through its oscillatory motions. Each expansion of the roof, therefore, is accompanied by a considerable broadening of the zone in which fissuring takes place. Since the crustal rocks can transmit compressional stresses much greater distances than they can tensional stresses, it is likely that the shrinkage and compression, which develop with each roof collapse, will be transmitted to whichever area happened to be sufficiently weak to yield to the compression of the first roof collapse. It is probable that this weak area would be a region somewhere out at the periphery of the Blister, where tension, during the first uplift, produced fissuring, but where the Blister materials were not sufficiently close to the surface to rise along the fissures and seal them, restoring their original strength. Thus, we see developing around some part or around the entire Blister a trough-like region. The width of this trough might well be a hundred or hundreds of kilo-

meters, and the depth would continue to increase as long as the Blister pulsations continued. Successive uplifts of the Blister roof would be apt to produce a thinning or necking of the crust in the geosynclinal region.

The geosynclinal region might or might not be adjacent to a land mass. It might be in the sea or it might be on land. There is no strong reason for preferential development in any one type of topographic area or lithologic area. If sedimentation does occur, the weight of the sediments would augment the continued down-sinking of the trough. This prevailingly downward

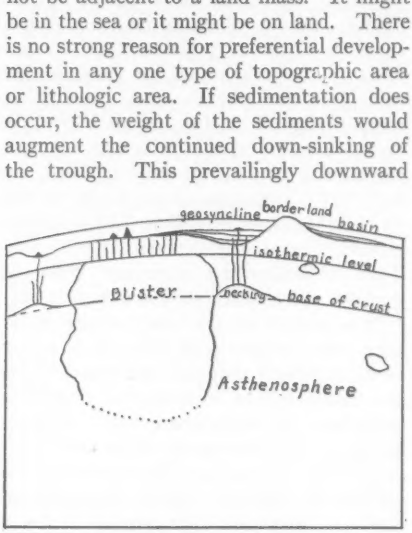

FIGURE 4. Geosyncline phase with volcanism into sediments. Continued volcanism above blister.

motion would, also, be increased by intrusions of basic magma, which would enter the geosynclinal sedimentary prism along fissures produced by an expanding phase of the neighboring blister. The nature of these intrusions would depend on the specific region in which the geosyncline developed and on the depth to which fissuring proceeded before the pressure release on the asthenospheric material was adequate to change that material to magma. Any down-sinking of the geosyncline would be accompanied by a stretching, continued necking, and weakening of the basement upon which the collecting sediments were resting (FIGURE 4).

Disturbances. It is obvious that after a geosyncline with sedimentation has been initiated, subsequent behaviour of the Blister roof must necessarily have a profound effect upon the bordering geosyncline. Each expansion of the roof will mean a continued stretching and down-sinking of the trough, and each collapse will mean a folding of part of the trough. Thus, a series of localized *disturbances* will develop, as, for example, in the overall history of the Alps or of the Coast Ranges. If the Blister be beneath the ocean, each expansion of the Blister roof would cause a flooding of the lands of the earth, and cyclical epicontinental sedimentation would accompany sedimentation in the trough.

Revolutions. The occurrence of a revolution, that is, the crumpling of most of the sediments of the geosyncline, does not occur, however, until very special conditions are obtained. The alternately expanding and contracting Blister must perforce grow laterally, since it cannot develop above the isothermic level. Eventually the heated Blister area will reach the basement region of the unstable geosyncline, which is capped by sediments with low heat conductivity. The thermal gradient becomes considerably steepened, and regional metamorphism of the lower geosynclinal sediments begins. It is important to realize that the recrystallization of the sediments is not the simple result of increased thermal gradient. The connate waters which are heated with the sediments act as media of molecular and ionic movement, and considerable migration is facilitated. The various zones of metamorphism depend, then, on the distance from the heat body and upon the amount of connate water present. In the presence of increased temperature, the waters will undergo considerable convection, which explains the enrichment or impoverishment of the various zones in various elements (FIGURE 5).

If the temperature of the connate waters approaches low temperature, magmatic conditions, a reversal of Bowen's reaction series takes place, and the alkali-, silica-rich portions of the rocks are dissolved therefrom, leaving the ferro-magnesian-

calcic portions intact. If there be no migration of the newly dissolved materials, a *lit-par-lit* phenomenon results. But, if migration is induced by growing pressures in the geosynclinal area, wholesale granitization effects may be observed, and large quantities of hybrid magmas may be produced. Concomitantly with this process, ore substances which were present in the connate water and in the sediments are redissolved and form ore fluids in the new magma.

The existence of such large quantities of heated connate water in the geosynclinal prism further weakens the section, and the stage is set for a tremendous revolution upon the next collapse of the Blister. This collapse is hastened by the weakening of the geosynclinal sector, and is complete rather than partial, which was the case when magma was intruded into and upon the roof. By the time of the major collapse, the crust above the Blister may have lengthened by as much as 20 miles, and this lengthening must be manifested by a crumpling of the geosynclinal and bordering sediments. This shortening is augmented by vast quantities of palingenetic and asthenospheric magma which are forced into the geosyncline by the weight of the down-sinking Blister roof. The apparent shortening is further increased by the extensive thinning and flowage of the sediments in the zone of intense metamorphism.

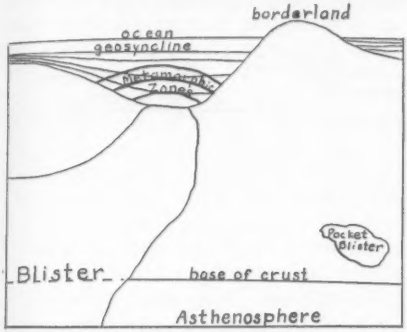

FIGURE 5. Beginning of metamorphism and preparation for orogeny.

The compression is manifested in five ways (FIGURE 6). The inmoving basement from the Blister direction may slide beneath the surface of the basin deposits. This produces a *décollement* and a wrinkling of the sediments, resulting in marginal folds. Overthrusting on a large scale proceeds at the surface of the geosyncline, but, in depth, the rocks yield plastically because of their conditioning by heated connate waters. Any platy minerals which have been formed, or are forming, by recrystallization become alligned, either as growth response to pressure environment or by flowage thereafter. This alignment is perpendicular to the direction of greatest pressure. Most of the yielding by flowage will be geocentric, and roots of considerable magnitude will be forced into the asthenosphere. Not only the geosynclinal sediments but also the basement will be involved in this downward thrust of sialic materials into the heavier asthenosphere. Even the less dense upper portion of the asthenosphere may be forced downward. Large scale syntectonic magmatic intrusion is the fifth manifestation of the compression.

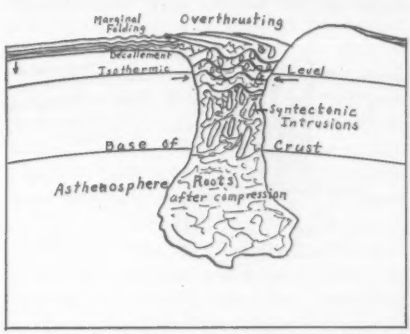

FIGURE 6. Compressional phase with formation of roots.

Isostatic Adjustment. It is of little importance whether the down-forced lighter materials remain solid with strength or liquid without strength. They will serve as buoyant masses which tend to rise toward the surface. It is not to be expected that the entire down-forced area will rise

uniformly. Rather, the brittle upper portion will break into a series of blocks, each of which will rise differentially. Post-tectonic intrusions of the discordant type will be developed prior to and during the uplift. During the first stage, these intrusions will be more acidic and of palingenetic origin. The later intrusions will be developed from deeper-seated origins and will be more basic (FIGURE 7). Of course, differentiation of any one magma chamber may result in a succession of progressively more acid intrusions.

The rising of the fault blocks, although the result of tension, will be along steep angle reverse faults, since this arrangement permits movement with the least amount of force; and, since the faults are of the reverse type, fractures will open and magma from depth will rise to the surface, producing the typical volcanism associated with fault block mountains.

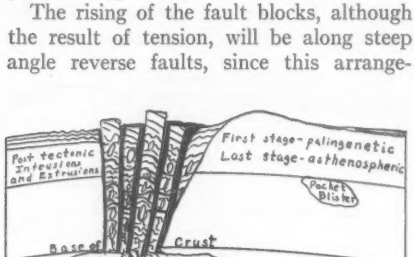

FIGURE 7. Isostatic uplift and fault block phase

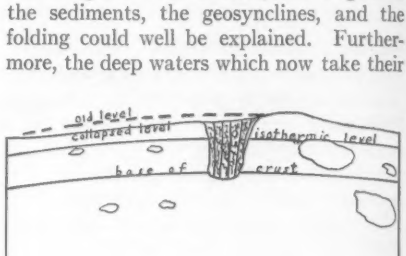

Figure 8. Erosion and quiescence with formation of new pocket blisters.

During the first stage of isostatic uplift, uplift exceeds gradation, and high mountainous areas develop, the ruggedness of the mountains being primarily due to erosion. In the last stage, the rate of uplift is much less than the rate of gradation, the region begins to approach sea level once more, and a stage of quiescence is begun. At the same time, new Pocket Blisters have been forming, either in the same region as before or in other areas, and another cycle is in the making (FIGURE 8).

Possible Examples. The hypothesis is not developed as yet to such perfection that one can point with complete assurance to precise examples of the Blister Cycle. A few suggestions, however, may be made. During the Paleozoic Era, there were four borderlands contributing sediments inland into what is now North America and Greenland. Appalachia, Llanoria, Cascadia, and Arctica are now deep water, and inland from each of these there are now exposed ancient folded mountain belts. If these regions were blisters, the origins of the sediments, the geosynclines, and the folding could well be explained. Furthermore, the deep waters which now take their place may be explained on the basis of a considerable collapse of the Blister areas, the roofs of which were highly intruded by heavier magmas. If this thought is correct, the permanence of continents and ocean basins, except for the Pacific, must be greatly doubted.

The history of the Paleozoic folding which surrounded the region of what is now the Atlantic is typical of what might be expected if a Blister in the Atlantic region were responsible for the geosynclines of the Paleozic Alps, the Scottish Highlands, the New England-Acadian area, and the Appalachian area. The Caledonian revolution began in late Silurian time in Scotland, followed by a somewhat later collapse in upper Devonian time in the New Eng-

land-Acadian region, and in the Paleozoic Alps and Appalachian troughs in Permian time. A series of closely spaced orogenies in areas which form parts of a great arc around a common center is best explained on the basis of the growth and collapse of a Blister in that center. This may well explain the development of the great belt of negative anomalies, of mountains, and of volcanoes which now surround the Borneo region in the East Indies. According to the hypothesis, this belt is a recently compressed periphery of a Blister. The present phase represents an isostatic uplift of the root areas. The various depths of focus of quakes in adjacent areas depends in large measure to the degree of completion of isostatic uplift and on the magnitude of the root areas.

Africa represents an unusual continent in its high average altitude and in its rift line with associated volcanism. The existence of a blister beneath the African region is the most satisfactory explanation for these unusual phenomena. Generally speaking, surface volcanism is the result either of tension above a blister or of tension along reverse faults during isostatic uplift, and it is not very difficult to decide which of these two is operating in the various volcanic areas of the world today.

The great linear mountain ranges of the earth, such as the Andes, represent a folding of simple geosynclines. Such mountain complexes as the Himalayas, however, must be explained on the basis of the coalescence of possibly as many as three blister margins in one area, producing unusually large roots with the subsequent great uplift and complexity of development.

Other examples might well be urged at this point, but the above will suffice to give the general picture. Much study of a quantitative nature must be made on such problems as heat conductivity of rocks under various conditions of temperature and pressure and distribution of radioactivity in the crust. Paleogeography can be reconsidered in the light of the hypothesis and should prove a valid test for its proposals. The foregoing paper has been necessarily shortened, and many important details have been omitted, but the general principles have been outlined. The author is not completely satisfied, but in so far as he has been able to apply the hypothesis to the known facts of orogenesis, metamorphism, petrogenesis, and related geological phenomena, he is convinced that something of the sort must serve as the unifying principle which will integrate the many great problems of the crust.

SECTION OF BIOLOGY

THE TREATMENT OF HUMAN THYROID DISEASE WITH RADIOACTIVE IODINE

By J. B. TRUNNELL*

There is an irreducible minimum of nuclear physical knowledge and terminology which must be defined and understood before any intelligent discussion of clinical or other biological application of isotopes may be undertaken. *Isotopes* are substances having identical atomic numbers but different atomic weights. They may be stable or unstable. The latter are called radioactive.

It will be recalled that all atoms are composed of protons, neutrons, and electrons.† *Protons* and *neutrons* are collectively known as *nucleons* because together they make up the nuclei of atoms. Protons and neutrons (which have essentially the same mass) together contribute, for all practical purposes, the *atomic weight*. Neutrons bear no charge. Although much "heavier" (1838 times) than an electron, the positive charge of a proton

* Memorial Hospital, New York, N. Y. This paper was the first of three papers presented on the subject, *Biological and Clinical Studies with Radioactive Iodine*, at the meeting of the Section on March 14, 1949.

† No doubt a gross oversimplification, but convenient for descriptive purposes.

exactly counterbalances the negative charge of an electron. The number of protons in the nucleus of an atom (and consequently the number of electrons around the nucleus required to balance the charge) is known as the *atomic number*. Factors closely concerned with the atomic number determine the chemical characteristics of a substance. The atomic weight of an atom may vary (according to the number of neutrons) without changing the chemical characteristics, provided the atomic number is not altered.

The element hydrogen, with its isotopes, provides a good example of these phenomena. Hydrogen has an atomic number of one and an atomic weight of one, since its nucleus is composed only of one proton. Certain of its chemical characteristics are well known and include the ability to combine with oxygen or halogens to form water or acids. If a neutron is added to the nucleus of a hydrogen atom, the atomic number remains unchanged, but the atomic weight is doubled. The resulting atom will be a stable isotope of hydrogen known as deuterium or heavy hydrogen. This substance is chemically indistinguishable from ordinary hydrogen and participates in chemical reactions exactly as does hydrogen. Deuterium is a stable isotope, since the nuclear configuration does not change spontaneously. If, on the other hand, an additional neutron is added to the nucleus, thereby increasing the atomic weight to three, while preserving the atomic number of one, still another isotope of hydrogen is formed. This nuclear composition is not "satisfactory" and will re-arrange itself to achieve a more stable ratio of protons to neutrons. In the process of re-arrangement, a particle is ejected from the nucleus at high speed.

For the sake of convenience, a neutron can be thought of as dividing into a proton and electron. However, the presence of an electron in the nucleus itself is apparently not tolerated. Consequently, as soon as the electron is formed, it is forcibly ejected at a speed which may approach the velocity of light and is known as a beta particle or a beta ray. A few millionths of a second later (not in radioactive hydrogen, but in many radio isotopes), there may also be emitted a packet or quantum of energy in wave form known as a gamma ray. The residual proton obviously increases the atomic number by one. Hence, the atom is no longer one of hydrogen, but has become an isotope of helium, the only element which has an atomic number of two.

The term *curie*, as employed in isotope parlance, defines a quantity of potentially radioactive atoms in terms of a rate of nuclear transformation, which rate is, numercially, 3.7×10^{10} transformations per second. A millicurie is 1/1,000th as much (the quantity in which there are 3.7×10^{7} transformations per second), whereas a microcurie is 1/1,000,000th as much (3.7×10^{4} t/s).

Half life is a convenient phrase designating the period during which one-half of a given large quantity of potentially radioactive atoms will have undergone nuclear transformation. Iodine 131, for example, has a half life of eight days, which means that of any quantity measured on this date, only half the quantity will remain after eight days. After sixteen days, one fourth will remain. After twenty-four days, one eighth will still have failed to undergo nuclear transformation. The half life of any given isotope cannot be influenced by any alterations of temperature or chemical combinations, unless the nuclei of the atoms themselves are changed (as may occur in a carbon uranium pile or in a cyclotron). The half life period may vary enormously from one element to another or among isotopes of the same element. Isotopes are known which have a half life of only a fraction of a second, whereas others have half lives of many thousands of years.

Specific activity is an expression of the number of millicuries (or curies) per unit weight of material. The specific activity of some isotopes is impressively high. For example, the largest single therapeutic dose of radioactive iodine, 315 millicuries, weighed approximately 2.5/1,000,000 of a gram. This quantity, which is too small

to visualize without the aid of optical equipment, is only slightly greater than the amount of stable iodine which is normally present in a tumblerful of New York City tap water.

Almost the entire usefulness of radioactive isotopes in tracer or therapeutic studies depends upon three fundamental characteristics:

(1) Because isotopes have identical atomic numbers and hence identical chemical behavior, radioactive atoms of a given substance will undergo the same chemical reactions as the more familiar stable isotopes. Hence, other chemical substances and even biological systems cannot differentiate one isotope from another, and will utilize atoms of each in direct proportion to their percentage composition in any given mixture of two or more.

(2) Radioactive atoms can be detected conveniently by means of relatively simple physical equipment. Depending upon whether or not gamma rays (long range) or beta rays (short range) are emitted, detection can be accomplished at a point outside the intact body. Highly accurate quantitation of quantity per unit volume or unit weight is usually possible.

(3) The speeding particles emitted from the nucleus produce effects in tissue which are, in the final analysis, similar to the effect produced by X-rays or by the gamma rays of radium. It is well to recall that X-rays or gamma rays do not primarily influence tissue, but do so indirectly by knocking high speed electrons from atoms of tissue itself. These electrons, being capable of ionizing molecules through which they pass, produce tissue damage which, within rather well defined limits, is a function of the amount of energy absorbed by the tissue.

This amount of energy absorbed has been used as a basis for calculation by Marinelli of a tissue dose in equivalent roentgen units for a variety of isotopes. Iodine 131, which has been used most extensively in these studies, delivers 158* equivalent roentgen units per microcurie of iodine per gram of tissue (assuming that there is homogeneous distribution of the isotope in the tissue and that the isotope remains during its entire duration of decay). It can be said, therefore, that, theoretically, very large quantities of radiation may be delivered to tissue when a radioactive isotope is selectively absorbed and retained. For example, if 500 microcuries of Iodine 131 were to be deposited in each gram of a given quantity of thyroid tissue, 79,000 equivalent roentgens would be delivered in the tissue, providing the iodine was not metabolized and secreted.

Several factors operate, however, to prevent the actual realization of such tissue doses. First, and perhaps most important, there is not homogenous distribution of the isotope in the tissue. This spotty type of distribution can best be seen by examining a radioautograph.† Secondly, thyroid cancer which is differentiated well enough to collect iodine is, also, usually capable of making some thyroid hormone or a reasonable facsimile thereof. Accordingly, iodine which is collected does not remain in the tissue during its entire period of physical decay, and upon being secreted is obviously no longer capable of radiating the tissue. Hence, the calculated dose is diminished further. A third, and equally important factor, has to do with the fact that cells at the periphery of any mass of tissue are not being radiated from all adjacent cells, as are those deeper in the tumor. Hence, the calculated dose is again reduced in these areas by a factor of at least two. Despite these limitations, impressive quantities of radiation can be and have been delivered to normal thyroid, hyperfunctioning thyroid, and malignant thyroid tissue.

Until fairly recently, radioactive Iodine 131 was prepared by neutron bombardment of tellurium with subsequent chemical separation of the two materials. Now, however, it has been found feasible to sepa-

* This figure used by Quimby to replace older value of 147 equivalent roentgens.

† Made by excising tissue from a patient previously given radioactive iodine, fixing and sectioning in the usual way, and, then, exposing radiation sensitive (photographic) emulsion. After an appropriate period of exposure, the photographic emulsion can be "developed" and will show areas of blackening which correspond to areas of radio isotope concentration in the tissue section.

rate radioactive iodine from other uranium fission products as a by-product of pile operation. Radioactive iodine thus prepared is carrier free (that is, there is no admixture with stable iodine) and, in recent months, has become tellurium free also. There is, however, some contamination with another radio isotope of Iodine 133. This isotope, however, has a short half life of only 22 hours, and the degree of contamination is not great, particularly after time has elapsed in transit. Shipment is routinely by air freight, and the material arrives safely enclosed in lead-shielded containers. Iodine 131 is supplied as sodium iodide already in solution in distilled water.

After appropriate dilution, the material can be administered to animals or patients either by injection or orally. For the vast majority of human administrations, the oral route is preferable, although, for certain types of studies involving iodine metabolism, more reproducable results can be obtained by intravenous injection.

As has already been pointed out, the quantity of iodine in solution at the time of administration, even with large doses, is very small. Consequently, there is no taste, and the patient is unaware that he or she is taking anything but plain water. Before iodine was supplied from fission in the pile, there was appreciable contamination with the element tellurium. This substance imparts a characteristic garlic-like odor to the breath of persons receiving therapeutic quantities, but, is, of course, no longer a contaminant.

In so far as is known, no organ or tissue has the same high degree of selective concentrating ability for any element or compound as that exhibited by the thyroid for iodine. It is not at all surprising, therefore, that as soon as radio isotopes of iodine were available, they were eagerly pounced upon by investigators of thyroid physiology. Since that time, there has been rapid progress both in the acquisition of knowledge regarding iodine metabolism and in the evaluation of radioactive iodine as a therapeutic tool.

The treatment of hyperthyroidism can be accomplished with much smaller doses than those required in cancer. Because of the very nature of gland activity in hyperthyroidism, the tissue collects much more iodine than does a normal or neoplastic thyroid. Hence, in a general sense, the overall dose required is an inverse function of the rate of turnover of iodine, and is a direct function of the total mass of tissue to be irradiated. Depending upon the degree of hyperfunction and gland size, satisfactory control of hyperthyroidism can usually be accomplished with doses of from four to twelve millicuries of Iodine 131. Doses employed in the treatment of thyroid cancer, however, range from fifty to three hundred or more millicuries. In both conditions, it is preferable to have patients receive a low iodine diet for several weeks prior to treatment, in order that undue dilution with stable isotopes be avoided. Otherwise, the urinary excretion of the administered material will be unnecessarily high. If the patient has been receiving any of the antithyroid drugs, they should be discontinued for forty-eight hours before preliminary testing or before therapy.

A rapid survey of the conditions of iodine collection and renal excretion in any given patient can usually be accomplished by giving a small "excretory" dose, usually about twenty microcuries by mouth. Complete collections of urine in twenty-four hour periods for two days should then be made. Measurement of the quantity of radioactive iodine excreted provides a good clue because of the reciprocal relationship existing between collection by iodine metabolizing tissues and the renal excretion of iodide. Misleading results will be obtained if the patients have been receiving iodine or iodine-containing compounds, such as those used for gall bladder visualization, in which case the urinary excretion of iodine will be falsely high.

In the event of hyperthyroidism, therapy may proceed with only the urinary excretion data and an estimate of the gland size as determinants of dose size. According to Chapman, one should endeavor to deposit about 150 microcuries per gram of

estimated weight of thyroid tissue. Hence, in an individual with a gland estimated to weigh 50 grams, who has shown by a previous excretory dose that the urinary excretion will be 15 per cent, the total oral dose to be given can be calculated by multiplying 50 by 150 and by adding the 1.4 millicurie to be lost in the urine. The assumption is made, of course, that the 7,500 microcuries remaining in the body will all be in the thyroid. This is not strictly true, but, by setting 150 microcuries per gram as a minimum, sufficient allowance has been made to permit the delivery of adequate radiation in the gland. Following dosage of this type, the patient may be expected to achieve a euthyroid state after about six weeks.

Though enthusiasm varies from one institution to another for the use of radioactive iodine in the treatment of Graves' disease, there are sufficient theoretical considerations to argue against its widespread employment, particularly when surgical management of the disease in patients properly prepared with thiouracil and iodine has become eminently satisfactory in a great majority of cases. The possibility of the development of neoplasms fifteen or twenty years after radioactive iodine therapy should preclude its use in all but elderly or otherwise bad risk patients for surgery. There are, no doubt, isolated cases in which unusual circumstances also justify use of Iodine 131. A somewhat different philosophy is permitted in dealing with cancer of the thyroid, although this term connotes variations between such wide limits of morbidity and mortality that much room for controversy exists.

There is almost no doubt however that radioactive iodine should *not* be employed as the only or first therapy in early or uncomplicated cases of thyroid malignancy. Cancer which is localized to the neck, even though extensive node metastases may be present, should be treated by radical surgery. Radioactive iodine, with rare exceptions, should be limited to those cases in which there are extensive or distant metastases in inaccessible places.

Of primary importance is the matter of whether or not these metastases collect iodine. There is some difference between figures obtainable from radio autographic studies (50%) and those obtainable from external body measurements (15–20%), with regard to percentage of otherwise suitable patients who are initially treatable with radio iodine. Although the former figure is higher, there is now adequate demonstration of the fact that a number of procedures are available not only to increase the latter figure, but, also, to increase the amount of iodine collected. These will be described below.

Any patient in whom isotope therapy of this type is contemplated should undergo a meticulous and complete clinical and laboratory examination. One should not rely upon the Geiger tube to locate metastases. Instead, a complete radiographic survey should be made. Repeated counts of red cells, white cells, total and differential, platelets, reticulocytes, hemoglobin, hematocrit, sedimentation rate, sternal marrow examinations, cholesterol, basal metabolic rate, and blood iodine levels should be made. Iodine intake should be restricted, but the ubiquitous distribution of iodine in food makes an iodine-free diet highly impracticable. Sea foods are specifically prohibited, and non-iodized salt should be used.

A small "excretory" dose of only a few microcuries (depending upon sensitivity of counting equipment available) can be given to determine the expected loss of larger doses of iodine in the urine. When this figure has been determined, a test dose of 200 – 500 microcuries should be given. Forty-eight hours after giving such a dose, measurements can be made over previously localized metastases. The major difficulty in determining the overall size of the therapeutic dose to be given lies in the lack of knowledge concerning the minimum cancercidal dose for various types of thyroid tumors.

Experience with X-ray therapy provides a rough basis for estimating the ideal dose goal. Certainly, where possible, one should endeavor to deliver no less than a total of

6,000 roentgens. Difficulties already described in achieving uniform distribution of radiation in these tumors do not permit uncorrected use of the expression "158 equivalent roentgens per microcurie per gram." Allowance must be made for spotty distribution of the isotope, for "edge effects," and for metabolism and secretion of iodine, all of which tend to reduce radiation in some or all areas of the tumors. No precise opinion can be expressed to cover all contingencies. However, if one even hopes for "destruction" of malignant tissue, a factor of at least six should probably be applied. Hence, instead of 6,000 roentgens, a more proper goal may be approximately 40,000 equivalent roentgens. Therapy is no doubt worth undertaking if these figures seem unattainable, but hope of tumor ablation should be guarded. Final calculation of the total oral dose depends, as in hyperthyroidism, upon previously determined renal excretion and upon estimated tumor weight and measured tumor iodine collection. In a hypothetical case in whom renal excretion for the first ninety-six hours totals 45 per cent and in whom exists an estimated one hundred grams of metastatic cancer, which has been shown by external readings to collect approximately 15 per cent of a test dose, the following considerations are of importance. To deliver 40,000 equivalent roentgens, it will be necessary to deposit about 250 microcuries per gram of estimated tumor weight. The entire quantity of Iodine 131 to be taken up by the aggregate metastases is then 100×250 microcuries or twenty-five millicuries. The total dose is then $\frac{25 \times 100}{15}$ or 166 millicuries. This is within the range of doses which have been given without immediate or apparent undue effects on normal tissues (single doses of 315 have been given). However, the above case represents a quite favorable setting seldom encountered.

In less suitable cases, it seems advisable to attempt to improve the ability of the metastases to collect iodine, even though several months may elapse prior to the administration of Iodine 131 therapeutically.

Four procedures have shown more or less promise as means of improving iodine collection:

(1) Thyroidectomy (either surgical or "medical" with radioactive iodine) has been followed in twelve of twenty-four patients by significant increases. Improvement in isotope pick-up is not sudden, but continues slowly to increase for several months. In some instances, the degree of increase has made therapy possible in patients previously unsuitable.

"Medical" thyroidectomy with radio iodine should be employed only in instances in which surgery is strictly contraindicated, since the latter is quicker, more certain, and does not use up any of the patient's overall total tolerance for Iodine 131. Further, considerable uncertainty surrounds the minimum effective dose for destruction of thyroid function. Doses as small as 15 millicuries have succeeded and doses as large as 70 millicuries have failed.

(2) Administration of relatively pure thyrotrophin* in doses of 30 milligrams per day has also been shown to increase collection of iodine and to diminish urinary excretion. The increase may be by as much as a factor of four or more. Therapeutic dose administration should be at forty-eight hours after discontinuing thyrotrophin, otherwise, a strongly refractory state may be encountered during which iodine collection is diminished, often to zero.

(3) Recently, very encouraging results have been obtained in a small number of patients given thiouracil for long periods. In one individual so treated, collection of iodine by multiple pulmonary metastases rose to more than 90 per cent of the total administered dose.

(4) Prolonged high grade water diuresis (suggested by Dr.s Alfred Gilman and Louis S. Goodman) has resulted in decreased urinary excretion and increased tumor pickup. Such diuresis must continue for a week and the daily intake needs to be

* Kindly supplied by Dr. John Mote of the Armour Laboratories, Chicago, Illinois.

kept at a minimum of eight liters. Iodine should be given, of course, just as increased urinary output has subsided after returning to normal fluid intake.

Results of therapy are difficult to interpret in the light of the relatively few cases which have been vigorously treated. No two have been handled exactly alike and, almost certainly, the maximum possible quantity of radiation has not been delivered in anyone. Repeated doses have been given to several patients, so that their total amount of ingested radio iodine approaches one curie.

Unequivocal improvement has been observed in a sufficient number of these patients to indicate the fundamental soundness and potential usefulness of the technique. Major effort is still being concentrated upon ways and means of improving iodine collection by these tumors, since the few really striking results have been seen only in patients with cancer of high concentrating ability. Decrease in pain and narcotic requirement, regression in varying degrees of palpable tumor, improvement in appetite and "general well being," gain in weight, and improvement in vision when impaired by lesions in the skull are among the more definite changes seen in one or more patients.

Complications and damage to normal tissues have been extensively anticipated, and, though evidence for their occurrence exists, it is perhaps more meager than originally feared. One patient, in generally poor condition, died with pancytopenia following several large doses of radio iodine. Others have shown varying degrees of bone marrow and peripheral blood depression. In some, despite substantial quantities of radiation, the bone marrow has returned to an approximately normal morphology. Three female patients in their late thirties have ceased to menstruate after treatment of thyroid cancer with radio iodine. No definite evidence is available to suggest damage to liver, kidneys, or other organs. Little comfort should be derived from the present paucity of normal tissue damage, however, since the long latent period of radiation damage onset is well known.

An acute thyrotoxicosis has been observed to follow treatment in several patients. This complication is presumed to result from sudden release of previously stored hormone when confining cells are destroyed by radiation.

In individuals with low cardiac reserve, this constitutes a real hazard. Such individuals should probably be given thiouracil for two months, in the hope that, thereby, most of the hormone stored in the tumor may be gradually released before radiation is given.

The entire subject is still in the earliest stage of development. Experience, even in the busiest centers of investigation, is woefully inadequate for the formulation of conclusions or of hard and fast opinions. All that has been expressed in this review is, therefore, subject to revision. Time and continuing investigation will provide more tenable points of view in this currently limited, but potentially large field of therapeutics.

DEGENERATIVE AND REGENERATIVE CHANGES IN THE THYROID GLAND FOLLOWING HIGH DOSAGES OF RADIOACTIVE IODINE

By AUBREY GORBMAN*

The employment of radioiodine as an injurious agent for control of thyroidal overactivity or cancer has prompted interest in the degree of thyroidal injury to be expected from a given amount of I^{131}. Another significant possibility attending use of this radioisotope is the injury of neighboring tissue by radiation emanating from the thyroid gland.

For experimental study of this problem, C_{57}- and CFW-strain mice weighing between twenty to twenty-five grams,

* Department of Zoology, Barnard College, Columbia University, N. Y. This paper was the second of three papers presented on the subject, *Biological and Clinical Studies with Radioactive Iodine*, at the meeting of the Section on March 14, 1949. This work was aided by a grant from the National Cancer Institute, U. S. Public Health Service, and by contract with the Atomic Energy Commission and the Office of Naval Research.

whose thyroids had an average weight of about five milligrams, were used. They were injected subcutaneously with 100, 200, 400, or 1,000 microcuries of I^{131}. In a separate study, it was found that, under conditions of diet and maintenance in our laboratory, uptake of injected radioiodine by the thyroid was between 5 per cent and 10 per cent, and reached a maximum between 12 and 24 hours, for the 100 and 200 microcurie doses. No such study has been made with the higher doses. After reaching a maximum value, the thyroidal I^{131} concentration was dissipated at slightly different rates, depending on the dose given. The "biological half-life" in the thyroid was about two days. Calculated roughly from such data, and as though the mouse thyroid were a large piece of tissue, the radiation dose was about 26,000 equivalent roentgens for the 100 μc. dose and 75,000 e. r. for the 200 μc. dose. Since the dimensions of the mouse thyroid are of the same order as the travelling range in tissue of β radiation from I^{131}, much of the β ionization is in neighboring tissue. Consequently, the above calculation of intrathyroidal equivalent roentgens delivered by a certain concentration of I^{131} is probably much higher than actual for the mouse thyroid, which in no place is more than a millimeter thick.

Mice were sacrificed at intervals of 2, 3, 7, 24, 120, and 300 or more days after administration of radioiodine. Animals given 1000 microcuries never survived beyond one week. Those given 400 microcuries usually died before one month. All thyroid glands were removed in contact with the trachea and were completely sectioned serially. A few of the long-term animals were given a second tracer dose of 10 microcuries 24 hours before autopsy and radioautographs were made of sections through the thyroid region.

Short Term Effects. The severity of injury to the thyroid after two or three days varied from minimal to complete destruction within the 100–1000 μc. range of dosages. The 100 μc. animals killed after 2–3 days (having yet received only a fraction of the total possible radiation) revealed thyroidal injury only upon careful study. In these, small centers of pycnosis of follicular cells appeared, especially in the medullary part of the gland. Parathyroid was apparently uninjured, but any thymic tissue near the thyroid was at least partly degenerate.

The 200–300 μc. dosages produced more extensive epithelial pycnosis as well as vacuolization. Many thyroidal cells were enlarged and contained large droplets of material similar to the colloid. Intrafollicular bleeding was not uncommon. Constant accompanying phenomena were periglandular edema and swelling of endothelial cells of intrathyroidal blood vessels.

The 1000 μc. dose at two days produced complete destruction of the thyroid and parathyroid tissue. Since destruction was so rapid, the follicular architecture of the thyroid was preserved, but all material, former cells and colloid alike, were amorphous in texture and uniformly eosinophilic. Only in a few places could very lightly staining nuclei be recognized. All tissues in the walls of thyroidal blood vessels were hyalinized and no stainable nuclei were evident. Yet, such blood vessels appeared to be carrying blood successfully. At seven days, active phagocytosis had removed most of the cellular debris resulting from such destruction and fibrotic changes, shrinkage, and small hemorrhages were evident.

Twenty-four-day Interval. Examination at this interval shows surviving thyroidal tissue only in the 100 μc.- and 200 μc.-dose mice. At this time, it should be remembered that virtually all of the ionizing radiation has been expended. Tissue surviving the 200 μc. dose is restricted to the cranial apex and the isthmus of the thyroid. Most of it is pycnotic, but some cells show a greatly hypertrophied cytoplasm despite variable degrees of nuclear pycnosis. Colloid next to such cells usually is well vacuolated, a change which is usually taken as a sign of secretory activity. The main part of the thyroid is represented by a shrunken

fibrous band, the edema having subsided. The 100 μc. dose permits survival, at this time, of a larger amount of thyroid, some even in the "body" of the thyroid, but only at the edge of the gland. A smaller proportion of cells is distinguishably pycnotic and more are in the hyperactive state.

120 to 400-day Interval. After 120 days, surviving thyroid is found only in 100 μc. animals. This is found as one or two small patches of follicles in a shrunken fibrous band of tissue. Surviving thyroid is very atypical in appearance. It is organized in small follicles or as nonfollicular masses. The cells are enlarged and of odd shapes and usually contain colloid-like masses. It is interesting that there is little or no difference between surviving thyroid masses of 120 days and those of 400 days, indicating absence of any tendency toward regeneration. Radioautographs showed that these glands do metabolize some iodine, but preliminary tracer studies indicated that the amount of iodine retained is relatively small. The relation of this amount to the mass of surviving tissue is difficult to determine. No neoplastic changes have been observed.

Summary. Under specified circumstances, 200 μc. or more of I^{131} cause complete thyroidal destruction in mice. Doses of 100 μc. permit survival of small bits of atypical thyroidal tissue, which even after 400 days show no tendency toward regeneration.

THE ZONE OF ACTIVITY OF ANTIBODIES AS DETERMINED BY THE USE OF RADIOACTIVE TRACERS

By DAVID PRESSMAN*

Since the turn of the century, attempts have been made to use antisera prepared against malignant tissues in the treatment of cancer.[1] Such antisera prepared against infectious agents have been found effective in combating the corresponding diseases, and it was reasoned that antisera prepared against cancerous tissue might be effective in combating cancer.

The sera were produced by injecting tissue homogenates or fractions of tissues into rabbits. The rabbits were then bled and the serum thus obtained used therapeutically. Unfortunately, the results obtained by the original investigators have been quite equivocal. The failures to obtain positive results may have been due to one or more reasons: (1) The serum contained no antibodies which would react with any part of the tissue. This is unlikely, since antibodies of some sort can usually be obtained by such a procedure. (2) The sera contained antibodies which cross-reacted with other tissues and were completely taken up by the other tissues. (3) The sera contained specific antibodies for components inside the tumor cells, but could not reach these intracellular components and effect them. (4) The sera contained antibodies which did localize in the tissue, but did not produce an observable physiological effect, and, since the results were actually dependent upon a physiological effect of the antiserum, negative results were recorded.

Actually, with transplanted tumors, it has been shown by Kidd,[2] Burmeister,[3] and Green[4] that exposure of the tissue to its homologous antisera before transplanting destroyed the ability of tumor tissue to propagate, and, here, we have evidence of a physiological effect of an antiserum.

In a reinvestigation of the field of tumor immunology, it seems reasonable that, first, it must be proven that there is something in an antiserum prepared against a malignant tissue which goes to the tissue in question. This can be accomplished by the use of radioactive tracers. If an antiserum against the tissue is prepared and the antibodies are tagged by coupling with radioactive substances or by having a radioactive elements incorporated in the antibody molecule, disposition of the anti-

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body, after its injection, can be traced by following the disposition of radioactivity. Further, it is not impossible that, if antibodies can be found which go specifically to a certain tissue, they can be made to carry physiologically active amounts of radioactivity to the tissue. Thus, reliance need not be placed upon the capacity of the antibodies themselves to produce a physiological effect.

Evidence has been obtained[5-7] that other diseases, such as glomerulonephritis, rheumatic fever, and multiple sclerosis, may be caused by the production of antibodies by an animal against his own tissues. The use of radioantibodies may well be important in tracing the course of these diseases. We have been able to prepare an antikidney serum and follow its course to the kidney. This is the work which I shall report here.[8-10]

The Effect of Coupling Various Substances to Antibodies on the Antibody Specificity

The fact that various substances can be coupled to antibodies without destroying the ability of the latter to combine with antigen has been shown previously.[11-15] Thus, as early as 1930, Reiner[11] showed that arsanilic acid can be diazotized and coupled to antibodies without destroying antibody specificity. It is not too surprising that this is possible, since the antibody molecule is very large, with a molecular weight of about 160,000, and the antibody specific region is, probably, just a small part of the surface of the molecule. Marrack[12] was able to couple a red dye to antityphoid serum and showed that the typhoid bacteria, when agglutinated with the antiserum, were colored red. The serum was labelled by coupling "R-salt" to one end of bisdiazotized benzidine and the serum to the other. Later, Coons, Creech, and Jones[13] prepared a labeled antipneumococcus type 3 serum by coupling the antiserum with β-anthrylisocyanate to form a serum containing β - anthrylcarbamido groups. Pneumococcus type 3 organisms, when agglutinated with this serum, showed a blue fluoresence. Then Coons, Creech, Jones, and Berliner[14] coupled fluorescein-4-isocyanate with antiserum against type 3 pneumococcus, and the pneumococci, agglutinated, showed a green fluorescence. They were able to show the presence of pneumococcus type 3 in tissues by means of this antiserum. Their technique was to sacrifice an animal heavily infected with pneumococcus type 3, prepare slides of the various tissues and stain the slides with the fluoresceins labeled antiserum. The regions of the tissue which showed the green fluorescence were considered to be those containing either the pneumococci or the specific polysaccharide. In all the labelings so far described, there has been a known definite chemical bond formed between the antibody and the material coupled. For instance, the diazotized compound coupled with the tyrosine and with the histidine to form an azo linkage and the isocyanates coupled with free amino groups of the protein to form carbamido linkages. McClintock and Friedman[15] "combined" uranium and malachite green with antibodies against pneumococcus polysaccharide and showed localization of the serum in regions which had been heavily infiltered with the pneumococcus polysaccharide.

For our work, we decided on the use of radioiodine 131 as a tracer. It has the advantages that iodine will directly iodinate the tyrosine and, probably, the histidine of a protein molecule, and this forms a definite bond with the protein molecule. It is easily obtained, easily counted, and has a convenient half life. Iodine has the disadvantage that it goes to the thyroid, but it is known that this can be controlled by feeding non-radioactive potassium iodide.

We have shown that it is possible to iodinate an antiserum, without destroying its specificity, by iodinating antiserum prepared against ovalbumin. That the antiovalbumin activity has not been destroyed is evidenced by the fact that such antiserum is precipitable by the specific antigen. That the antibodies in an iodinated antiserum

actually contain iodine and that the radioactivity is specifically precipitated are demonstrated by the following experiment: Antiovalbumin serum was iodinated by iodine containing a tracer amount of iodine 131. This iodinated antiserum was then mixed with antiserum prepared against beef serum coupled with diazotized para-aminobenzoic acid.[16] The resulting mixture was divided into two parts: to one was added ovalbumin; and to the other was added beef-serum azobenzoic acid. Both antigens were in the concentrations for optimum precipitation. Precipitates were obtained in both cases. In the case of the ovalbumin precipitate, there was a high level of radioactivity, and in the other precipitate there was practically no activity. This showed that out of the mixture something that was radioactive was brought down specifically by ovalbumin and not non-specifically by a non-specific system. Thus, the conclusion must be drawn that the antibody specificity was not destroyed and that the antibody molecules specific to the ovalbumin contained iodine.

The Preparation of an Antiserum Against a Tissue and the Tracing of the Antibody to the Tissue

The next step was the preparation of an antiserum against the tissue and tracing it to that tissue. For carrying out this step in our method, we selected to study antiserum which can be prepared against rat kidney. This antiserum was studied previously by Masugi,[17] and later, by Smadel and his coworkers,[18] and has been shown by these workers to possess definite nephrotoxic effects and to produce physiological changes in the structure of the rat kidney when administered intravenously into the rat. Since such a serum has definite effects on the kidney, it seemed logical that the antibody probably goes to the kidney, and, if the antibody were labeled, it should be possible to follow it to the kidney. We carried out this experiment by preparing such an antiserum against kidney tissue, according to the method of Smadel, and then separating out the globulin by fractional alcohol precipitation and subsequently iodinating with iodine containing tracer concentrations of I 131. By injecting several rats with this radio anti-kidney globulin and others with a similarly prepared radio anti-ovalbumin globulin as controls, waiting for about 4 days and then sacrificing the animals and analysing the various tissues, we found that there was a definite accumulation of iodine in the kidney. With anti-kidney serum, there is a very large uptake of radioactivity by the kidney, whereas with the antiovalbumin, there is practically no uptake in the kidney. This shows definitely that there is something present in the anti-kidney serum, presumably an antibody, and absent in antiovalbumin serum, which localizes in the kidney.

However, there is increased uptake by other organs when anti-kidney serum is administered, but to a much lower extent than is the increase by the kidney. This cross reaction is probably due to the presence of common types of tissue in the various organs, such as blood vessels, *etc.* There remains the possibility that the pickup of the radioiodine by the kidney is not directly due to the radio antibodies remaining in the kidney, but that it may be due to a non-specific effect of the anti-kidney serum to sensitize the kidney so that it can nonspecifically pick up various substances, such as radio-antibody or the radio-iodinated proteins other than antibody, which are injected at the same time. This possibility, although it seemed unlikely, was investigated and was found not to be the case.[9] This was demonstrated by inoculating one group of animals with a radio-iodinated anti-kidney serum, another group with radio-iodinated antiovalbumin serum, and a third group with a mixture of radio-iodinated antiovalbumin serum and a non-radioactive, but iodinated, anti-kidney serum. There was a pickup of radioiodine in the kidneys of the first group, but not in the second and third groups, showing that the non-radioactive kidney serum did not cause an alteration of the kidney so that it would pick up the radio ovalbumin.

We have since repeated our localization experiments using mice, with much the same results. We have further shown that the localization of the anti-kidney bodies is not a strain specific phenomenon, since the antiserum prepared against the kidneys of AKM mice will also localize in the kidneys of Rockefeller Swiss mice, A strain mice, C57 black mice, and Rockland Farm mice. Cross reaction with rat kidney has also been observed.[10]

Recently, we have obtained data concerning the duration of antikidney serum in the kidney as compared with other tissues. We have measured the rate at which the radioactivity in the various tissues disappears for a length of 54 days. When plots were made of the logarithm of the radioactivity concentration in the tissue against the time plotted lineally, straight lines were obtained in most cases. It was possible to follow the radioactivity in these experiments in the kidney for a period of 54 days and in the thyroid for 54 days, but the concentrations in radioactivity in the blood stream, spleen, and liver decreased too rapidly to permit the measurement over the long range of time. From the straight line curve, it was possible to calculate half-life for the retention of the carrier of the radioactivity. The half-life of the carrier in the kidney was 20 days; in spleen, 2.6 days; liver, 2.9 days; blood, 1.8 days; thyroid, 6.8 days; and the whole animal, 2.0 days. The long half-life of the radioactivity carrier, presumably the antibody, in the kidney, indicates that, apparently, the antibody has become attached to the cell in such a way that the enzymes of the cell or of the tissues cannot metabolize the antibody. This prolonged retention of radioactivity is greater even than the retention of iodine by the thyroid, and emphasizes the possibility of a radio therapy of cancer if specific antibodies can be found, since the duration of the carrier is so prolonged. The preparations of iodinated antibody which we have been using contain about 0.5 per cent of iodine. This means that 1 mg. of antibody protein, which can localize in the tissue, carries 5 micrograms of iodine and corresponds to about 600 millicuries of iodine, if all the iodine were radioiodine.

In order to determine the structures in the kidney which pick up the radioantibody, Miss Hill and Dr. Foote and I prepared radioautographs[19] of kidney sections obtained from mice inoculated with radioactive anti-kidney serum, in one case, and radioactive anti-mouse plasma serum, in the other case. There were definite regions of radioactivity concentrations in the kidneys of the anti-kidney serum-treated animals and no concentration with control animals. The radioactivity seems to have accumulated in a small punctate region, and we have found that the region corresponds to the glomerulus.

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DIVISION OF MYCOLOGY

THE ANTI-BORRELIA EFFECT OF BORRELIDIN

By M. BUCK, A. C. FARR, AND R. J. SCHNITZER*

It has been mentioned in the papers by Goldberg, Berger, and Jampolsky[1, 2, 2a] that the new antibiotic found and isolated by these investigators exerts a remarkably specific effect on borrelia, the spirochetes of relapsing fever. This activity seemed sufficiently impressive to give the name "borrelidin" to the newly found agent.

The purpose of the following technical remarks is to explain the experimental findings which support the facts presented by Goldberg and his associates.

As is well known, the borrelia infection of mice is not easily influenced by chemotherapeutic drugs. For many years, certain arsenicals and gold compounds were the only known substances capable of controlling an experimental borrelia infection. The high activity of penicillin in borrelia infections was first described, in 1943, by Heilman and Herrel[3] and has been confirmed by many authors since then. Recently, Heilman[4] found a similarly striking anti-borrelia effect with aureomycin.

The fact that there is only a comparatively small number of compounds with which the borrelia infection of mice can be successfully treated is one of the reasons why this infection is consistently included in the general screening schedule of our laboratory. In the course of the routine screening procedure, the anti-borrelia activity of borrelidin was found.

Before discussing the observations on the effect of borrelidin in the borrelia infection, it might be appropriate to describe briefly the other biological properties of this compound, particularly its toxicity.

TABLE 1 is meant to show that borrelidin is a comparatively toxic compound. Mice and young chicks were somewhat more resistant to the toxic effect of the antibiotic, but rats and rabbits were highly sensitive to it and so were humans. The main symptom of the acute poisoning was a hemorrhagic enteritis. Repeated administration of borrelidin required a considerable reduction of the dose. Even the more resistant mice and chicks did not tolerate more than 1.5 mg/kg over periods of 15–21 days. In dogs, the dose had to be reduced to 0.2 mg/kg and less.

It was surprising that even fractions of the small doses, which could be administered by the subcutaneous route, exerted a marked activity in the borrelia infection of mice. This is shown by the two examples in TABLE 2 and TABLE 3.

TABLE 1

ACUTE TOXICITY OF SINGLE DOSES OF BORRELIDIN

Animal	*Weight*	*Route of administration*	LD_{10} *mg./kg.*
Mouse	16 – 20 g	subcut.	74.7
		intraven.	39.0
Rat	80 –120 g	subcut.	1.78
Rabbit	2.5– 3.0 kg	intraven.	2.37
Chick	250 –300 g	intramusc.	>4.2

The tables present the results of the subcutaneous treatment with borrelidin administered 20–24 hours after an intra-abdominal infection. At that time, a manifest infection of the blood had developed. The data are based on daily examinations of the blood. In the later stages of the observation, the examination was occasionally omitted on a Sunday. The examples show that doses of 1.5 mg/kg in case of the very sensitive strain *B.* tick and 3.0 mg/kg in case of *B. Novyi* cured all mice and sterilized the brain. Doses of 0.75 mg/kg and 1.5 mg/kg, respectively, cleared the peripheral blood only temporarily, and relapses occurred in the majority of cases.

TABLE 4 gives a synopsis of our experiments on three strains of borrelia and indicates that all strains responded well to the treatment. The ratio LD50/CD50 was 125, 37, and 44 for *B.* tick, *B. Novyi*, and *B. Obermeieri*, respectively.

* Research Laboratories, Hoffman-La Roche Inc., Nutley, N. J. This paper, illustrated with lantern slides, was one of a group presented on the subject, *Borrelidin—A New Antibiotic*, at the meeting of the Division on March 25, 1949.

There was no definite influence of different dosage schedules on the effect of borrelidin. The data on the table are mostly based on a single subcutaneous administra-

relidin-like substances can also be demonstrated in concentrates from other sources than *Streptomyces Rochei*, for instance, from impure penicillin and from Clarase, an

TABLE 2

ACTIVITY OF BORRELIDIN IN *Borrelia* (TICK STRAIN)

Mouse no.	*Parasites in blood**	*Borrelidin† mg/kg*	*Days after treatment* 1–4	5	6	8	9–16	16–24
1	+		0	0	0	0	0	0
2	+		0	0	0	0	0	0
3	+	1.5	0	0	0	0	0	0
4	+		0	0	0	0	0	0
5	+		0	0	0	0	0	0
6	+		0	0	0	0	0	0
7	+		0	0	0	+		
8	+		0	0	0	0	0	0
9	+	0.75	0	0	0	0	0	0
10	+		0	0	+			
11	+		0	0	+			
12	+		0	+				
13	+		+++					
14	+		+++					
15	+	Controls	+++	Dead				
16	+		+++					

* Infection: ∞ 600,000 parasites intra-abdominally.
† Treatment: 1 day after infection; single subcutaneous treatment.

TABLE 3

ACTIVITY OF BORRELIDIN IN *Borrelia Novyi*

Mouse no.	*Parasites in blood**	*Borrelidin† mg/kg*	*Days after treatment* 1	2	5	7	9	16	20	*Brain transfer*
1	+‡		0	0	0	0	0	0	0	
2	+		0	0	0	0	0	+		
3	+	3.0	0	0	0	0	0	0	0	Negative
4	+		0	0	0	0	0	0	0	
5	+		0	0	0	0	0	0	0	
6	+		0	0	0	0	0	0	0	
7	+		0	0	0	0	0	0	0	
8	+		0	0	0	0	+			
9	+		0	0	0	0	0	0	0	
10	+		0	0	++					
11	+	1.5	0	0	0	0	+			
12	+		0	0	0	0	0	0	0	
13	+		0	0	0	0	0	0	0	
14	+		0	0	0	0	+			
15	+		0	0	0	+				
16	+		+++	Dead						
17	+		+++	Dead						
18	+		+++	Dead						

* Infection: ∞ 800,000 parasites intra-abdominally.
† Treatment: One day after infection; single subcutaneous injection.
‡ ∞ 650 per 100 fields.

tion of the antibiotic. Subdivision of the active doses into 2 to 4 treatments did not materially change the results, but, if the total dose was divided into 10 treatments with very small doses, a markedly lower effect was observed.

According to Berger's experience, borenzyme mixture used for inactivation of penicillin. These concentrates, which microbiologically appeared closely related to borrelidin, also possessed its anti-borrelia effect. This is shown in TABLE 5.

In this table the doses are given in units, because the weight of active material could

not be accurately determined by weight in the concentrates. Nevertheless, the comparison with crystalline borrelidin makes it quite evident that the activity of the substance contained in the Clarase was quantitatively identical with that of the pure antibiotic. Similar results were obtained with material from impure penicillin.

It was mentioned in the beginning of this paper that comparatively few compounds or groups of compounds show an effect in borrelia infections. It seemed of interest to determine whether the activity of borrelidin was biologically related to any of the known agents. The most suitable method for such an attempt is the use of a specifically drug-resistant strain.

TABLE 4

EFFECT OF BORRELIDIN IN EXPERIMENTAL INFECTIONS OF MICE WITH 3 DIFFERENT STRAINS OF *Borrelia*

*Strain Borrelia**	*Curative dose mg./kg.*	*Relapse dose mg./kg.*	*CD_{50} mg./kg.*
Tick	0.815	0.415	0.6
Novyi	3.25	1.06	2.0
Obermeieri	3.6	0.45	1.7

* Intra-abdominal infection with 400,000–500,000 parasites. Subcutaneous treatment.

In case of borrelia, this is not too easy a task. To our knowledge, no high degree of drug fastness toward any of the known drugs was ever achieved in borrelia, despite the efforts of many good and experienced investigators. Also, we were not very successful in our attempts to prepare a penicillin resistant strain of *B. Novyi*. A temporary reduction of penicillin sensitivity was obtained, however, and it could be shown that this strain responded normally to borrelidin.

It was fortunate that it was much easier to render *B. Obermeieri* resistant to borrelidin. Starting with an inactive dose of 1 mg/kg, a borrelidin fast strain was obtained in 40 serial passages with increasing doses, during which the strain became resistant to 30 mg/kg. This resistance was strictly specific, as is shown in TABLE 6.

The table is self-explanatory. All of the 4 other anti-borrelia agents are as active in the infection with the borrelidin fast strain as they are on the parent strain, thus indicating that borrelidin is a representative of another class of anti-borrelia agents.

We should also like to stress the point that the activity of borrelidin is limited to the anti-borrelia effect. It is a chemotherapeutic agent of particularly high specificity. Trypanosomal infections were not influenced by the antibiotic, and rabbit syphilis did not respond even to toxic doses. This was a very surprising observation,

TABLE 5

COMPARISON OF BORRELIDIN FROM *Streptomyces Rochei* AND FROM CLARASE IN *Borrelia Obermeieri* INFECTION OF MICE

*Compound from**	*Dose u./kg.*	*No. of mice*	*Number cured*	*Number relapsed*	*Number no effect*
Streptomyces Rochei	37,500†	6	4	2	0
Clarase	38,000	6	5	1	0
Clarase	19,000	6	2	4	0
Clarase	8,500	6	0	0	6

* Therapeutic experiment; single subcutaneous treatment.
† = 2.25 mg./kg.

TABLE 6

COMPARISON OF THE ACTIVITY OF MAPHARSEN, MYOCHRYSIN, PENICILLIN G, AND BORRELIDIN ON THE PARENT STRAIN OF *B. Obermeieri* AND ITS BORRELIDIN FAST MODIFICATION (BR-STRAIN)

Substance tested	*Active group*	*Minimal active dose: mg./kg. Parent Strain*	*BR Strain*
Mapharsen	As	6.25	6.25
Myochrysin	Au	25–50.00	50.00
Penicillin G	—	60.0*	60.0
Aureomycin	—	12.5	12.5
Borrelidin	—	1.5	30.0 (inactive)

* 4 treatments of 15 mg./kg.

because, to our present knowledge, all substances which are active in borrelia infections also exert an effect on *Treponema pallidum*.

There was, however, one interesting property of borrelidin with regard to the *T. pallidum* infection of rabbits, and this was the enhancement of the anti-syphilitic effect of penicillin G. It is known from the work of Rake and his co-workers[5] that impure penicillin showed a higher activity in rabbit syphilis than the crystalline material. As borrelidin might be one of the impurities present in crude penicillin, experiments were carried out by Soo-Hoo to study the in-

fluence of small doses of borrelidin added to crystalline penicillin G. The technique used was the determination of the protective dose of penicillin against an intradermal infection with *T. pallidum*, as recently suggested by Eagle, Magnusson, and Fleischman[6] and by Turner, Cumberland, and Li.[7] The rabbits were infected intradermally with 40,000 spirochetes and received a single intramuscular injection of penicillin or penicillin + borrelidin in an oil-beeswax mixture 24 hours after the intradermal infection.

There was a definite trend to increased activity if a small amount of borrelidin of 0.005 mg/kg was added to the crystalline penicillin G. The CD50 of crystalline penicillin G was 1.3 mg/kg; in presence of borrelidin, 1.2 mg/kg still protected the majority of animals (75%) and even 0.6 mg/kg was active.

Summary. Summarizing the experimental findings presented in this paper, it appears that borrelidin is a potent antibiotic with specific anti-borrelia activity. This effect was obtained with doses far below the toxic level of the substance. Although borrelidin was found to be without effect in experimental rabbit syphilis, there was a trend to enhancement of the anti-syphilitic action of crystalline penicillin G if borrelidin was added in small quantities.

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ENHANCEMENT OF PENICILLIN ACTIVITY BY BORRELIDIN

E. GRUNBERG, D. ELDRIDGE, G. SOO-HOO, AND D. R. KELLY*

Dr. Goldberg and his associates[1, 2, 2a] have pointed out the reasons which made them expect that borrelidin might be one of the factors responsible for the enhanced activity of penicillin G. One example, the enhancement of the anti-syphilitic action of crystalline penicillin G, has already been given.[3]

From the literature, it is known that increased activity of crystalline penicillin G by impurities has been observed in a number of experimental infections, even though no convincing clinical evidence of superior activity of impure penicillin is available. It might be appropriate to summarize the investigations that have already been carried out by different authors on the enhancement factors of penicillin G. These data may be observed in TABLE 1. Dunham and Rake[4] were the first authors to report an enhanced effect of penicillin G in the experimental treatment of rabbit syphilis. This was followed shortly by the work of Hobby *et al.*,[5] who showed the presence of enhancement factors of penicillin G in the experimental treatment of streptococcal and pneumococcal infection, by Welch and coworkers[6] in typhoid infections of mice, by Miller *et al.*[7] in the endotoxin poisoning of mice, by Cole[8] in the *in vitro* inhibition of trichomonas, and by Burk *et al.*,[9] who observed an enhancement effect of penicillin G in the inhibition of respiration of staphylococcus 209.

Before discussing borrelidin as a possible enhancement factor of penicillin G, it should be noted that the borrelia infection of mice was the only experimental model which responded to borrelidin. Included among the tests which showed no response to borrelidin *per se* are infections with β-hemolytic streptococci, pneumococci type 1 and 2, *Klebsiella pneumoniae*, *Salmonella schottmuelleri*, *Eberthella typhi*, *Mycobacterium tu-*

* Research Laboratories, Hoffman-La Roche Inc., Nutley, N. J. This paper, illustrated with lantern slides, was one of a group presented on the subject, *Borrelidin—A New Antibiotic*, at the meeting of the Division on March 25, 1949.

berculosis (*H 37 Rv*), influenza type A virus (PR8-strain), murine poliomyelitis virus (SK strain), rabbit syphilis (Nichols strain), *T. equiperdum* and *Cryptococcus hominis*.

A considerable amount of work was involved in our investigations in an attempt to prove the enhancement effect of borrelidin in the experimental models which have been enumerated in TABLE 1. We are now going to present the results of our experimental work concerning the study of the possible enhancement of penicillin G with borrelidin. We would like, first, to present all instances in which an enhancement activity of penicillin G was observed.

TABLE 1
COMPARISON OF PROPERTIES OF VARIOUS PENICILLIN ENHANCEMENT FACTORS

Author	*Typhoid*	*Strepto-coccus*	*Pneumo-coccus*	*Syphilis*	*Endo-toxins*	*Respira-tion*	*Tricho-monas*
Welch	X					X	
Hobby		X	X				
Dunham and Rake				X			
Miller					X		
Burk	—					X	
Cole							X
Borrelidin	—	X	—	(X)	(X)	X	X

(X) = trend towards enhancement.
X = Enhancement effect or inhibition of respiration of Staph. 209 (Burk).
— = No enhancement effect
Blank = No results available

A survey of our work with penicillin in streptococcal infections carried out during the last five years showed that the activity of penicillin G has remained practically the same since the time when the first batches of impure penicillin containing 100 units/mg. were tested in streptococcal infections of mice. The subcutaneous CD50 in those early experiments and in those from 1943 to the present time was between 300 and 500 units/kg. There was, however, one important difference. The less pure penicillin samples frequently maintained this CD50 with a single treatment, while the more recent and purer samples, which gave the same CD50, refer to two treatments with one-half this dose. The same effect of a single treatment with crystalline penicillin G required 3 to 4 times higher doses, the CD50 being between 1000 and 1500 units/kg.

Studies were, therefore, begun on the influence of borrelidin on the anti-streptococcal activity of crystalline penicillin G by using the single treatment method. These experiments were carried out with *Streptococcus hemolyticus C 203*. The infective dose was 0.5 ml. of a 10^{-5} dilution representing approximately 1000 MLD. A single subcutaneous treatment was given shortly after infection. Succumbing mice were autopsied and the blood cultured. Surviving animals were observed for 21 days, since, as is well-known, late death from streptococcus infection might still occur after 10 or 15 days and no experiment can be considered stabilized until 20 days have elapsed.

Needless to say, a very large number of animals was used before the optimal range of relationship of penicillin and borrelidin doses was found, even though suitable dosages of penicillin alone were known from previous experiments.

In TABLE 2 are the results of those small doses of borrelidin which, when combined with doses of penicillin giving only 40 per cent survival, increased the survival rate of mice infected with streptotocci. In this table, the results of a single subcutaneous treatment are given. There is a certain variation as to the optimal dose required to give the enhancement effect. It seems that the smaller the penicillin dose, the smaller will also be the optimal borrelidin dose.

If the CD50 of penicillin is calculated by the cumulative method of Reed and Muench[10] for all the groups of mice treated by a single subcutaneous injection, with and without borrelidin, a significant difference is

evident. The penicillin CD50 calculated on this basis is 0.56 mg./kg. for penicillin G alone and 0.25 mg./kg. for penicillin and borrelidin combined. It is interesting to note that this figure, 0.25 mg./kg. or 420 units/kg., is very close to the figure evaluated many years ago with impure penicillin. The material used in 1942–1944 was a sample combined from several experimental batches of a potency of 100 units/mg. In a streptococcal infection treated by a single subcutaneous injection, a CD50 of 300 units/kg. was obtained. These data

TABLE 2

ENHANCEMENT OF THE ACTIVITY OF PENICILLIN G BY THE ADDITION OF BORRELIDIN IN STREPTOCOCCAL INFECTIONS IN MICE

Penicillin		*Per cent Survivors* *Borrelidin*					
units/kg.	*mg./kg.*	*0* *0*	*3.125* *0.0002*	*6.25* *0.0004*	*12.5* *0.0008*	*25.0* *0.0017*	*units/kg.* *mg./kg.*
1500	0.9	40	—	60	100	79	
500	0.3	41.5	70	55	—	—	
250	0.15	40	—	60	—	—	

Controls: 1%.
Infection: 0.5 cc of 10^{-5} dilution intraperitoneally (Strain C203).
Treatment: 1 × subcutaneously.

the single treatment of a streptococcal infection is very close to the CD50 for treatment with 2 injections of 187.5 units/kg., which gives a final total of 375 units/kg., the question arose as to whether borrelidin also increased the activity of penicillin G given in 2 injections. This was indeed the case. In the experiment recorded in TABLE 3, which was carried out with streptococcus 4, 2 treatments with penicillin, 0.075 mg./kg., were given at four-hour intervals. This dose, which, as you can see, is well below the CD50 of penicillinG, alone gave 50 per cent survival if combined with 0.33 μg./kg. borrelidin. A statistical analysis of the figures has shown them also to be significant.

A number of experiments were also devoted to the question of enhancement of orally-administered penicillin in streptococcal infections. Here, as was observed in the subcutaneous treatment, small doses of borrelidin produced a marked increase of activity of penicillin G. The CD50 of penicillin G and 3 μg. of borrelidin per kilogram

TABLE 3

THE EFFECT OF PENICILLIN G AND PENICILLIN G PLUS BORRELIDIN ON STREPTOCOCCAL INFECTIONS *In Vivo*

Penicillin		*Borrelidin*				
units/kg.	*mg./kg.*	*0* *0*	*2.5* *0.00017*	*5.0* *0.00033*	*10* *0.00067*	*units/kg.* *mg./kg.*
125	0.075	8/30 =26.7%	10/30 =33%	15/30 =50%	11/30 =37%	

Controls: 0/30
Infection: 0.5 cc. of 10^{-5} dilution intraperitoneally (Strain: Strep. 4)
Treatment: 2 × subcutaneously

mean, therefore, that the addition of borrelidin restituted the original activity of less pure penicillin which had decreased in more highly purified and crystalline products of penicillin G.

We would like to emphasize the fact that the enhancement effect of penicillin G by borrelidin is only demonstrable if borderline doses of activity are used. Fully active and completely inactive dosages do not show the influence of borrelidin. This influence with borderline doses was statistically analyzed and a χ square value was obtained, corresponding to a probability (p) of considerably less than 0.001.

Since the CD50 of 420 units/kg. of penicillin plus borrelidin which was observed in was 0.7 mg./kg., in contrast to 1.16 mg./kg. of penicillin alone.

Before passing on to any discussion of other infections, we would like to point out that high doses of borrelidin interfered with the activity of penicillin which seemed to us to be similar to the hormetic effect described by Welch.[11] The majority of mice undergoing combined treatment by the subcutaneous as well as by the oral route died of the streptococcus infection if the ratio of penicillin to borrelidin was 1 to 0.3 or higher.

Another experimental model in which the enhancement effect of penicillin G by borrelidin was observed was the meningococcal endotoxin poisoning of mice. Meningococcus endotoxin was prepared according to

the method of Boor and Miller[12] and the animals received an intra-abdominal injection of from 0.4 to 0.6 ml. Two subcutaneous treatments were given before the injection of toxin and two more after the toxin injection, at intervals of two hours. The results are given in TABLE 4. PR8 as given in this table were old batches of impure penicillin containing 300–400 units/mg. This table shows that impure penicillin, PR8, was considerably more active than penicillin G, thus confirming the observation of Miller and his group.[7] The addition of a small dose of borrelidin also increased the activity, but to a lesser degree than that of PR8.

TABLE 4

ACTIVITY OF CRUDE PENICILLIN PR8, CRYSTALLINE PENICILLIN G, AND PENICILLIN G PLUS BORRELIDIN IN THE MENINGOCOCCUS ENDOTOXIN POISONING OF MICE

Drug	*Dose mg./kg.*	*No. of mice*	*Survivors No.*	*%*
PR8	4 × 50,000	30	16	53.0
Penicillin G	4 × 50,000	30	2	6.6
Penicillin G + Borrelidin	4 × 50,000 + 4 × 16.1 μg.	50	13	26.0
Controls	—	70	3	4.3

Endotoxin dose: 0.4–0.6 ml.
Treatment: 3–4 times, 2 treatments before, 2 after the endotoxin dose. Subcutaneous administration.

So far, this paper has discussed *in vivo* infections. At this point, a digression will be made to describe the only *in vitro* experiment in which an enhancement of activity of penicillin G by borrelidin was observed. We were able to confirm the findings of Cole,[8] namely, that impure amorphous penicillin exerted an anti-trichomonas activity at 2500 units/ml., while crystalline penicillin G was ineffective in concentrations greater than 10,000 units/ml. The addition of suitable concentrations of borrelidin, 0.0005–0.0007 mg./ml., which showed no appreciable growth inhibiting effect on trichomonas, resulted in an active dosage range of penicillin 1250–2500 units/ml., which equaled or surpassed the dosage range of impure penicillin.

Returning now to the *in vivo* models, experiments were also carried out with *Diplococcus pneumoniae* in which small doses of borrelidin were combined with various doses of penicillin G. The range of total doses of penicillin tested, as can be seen from TABLE 5, was between 0.3 mg./kg., which is an inactive dose, and 1.8 mg./kg., which cured 90 per cent of the animals. The results may also be seen in TABLE 5. This table shows that the lowest penicillin dose was not changed by borrelidin, and the same is true for the highest dose. The doses of borrelidin still seem quite high and should be titrated further. The variations, which are unavoidable, have been found to be insignificant.

TABLE 5

COMBINATION OF PENICILLIN G AND BORRELIDIN IN PNEUMOCOCCAL INFECTIONS OF MICE

Penicillin mg./kg.	*Borrelidin mg./kg. 0*	*0.3–0.5*	*0.75–1.0*	*1.5–2.0*	*3.0*
0.3	0/10	—	—	0/10	—
0.6	7/30[a]	0/10	0/10	6/20	—
0.9	31/50	5/20	17/30	25/40	4/20
1.8	18/20	9/10	10/10	—	—

Controls: 0/80[a]
(a) 7/30 = survivors out of 30 mice
0/80 = survivors out of 80 mice
Infection: 0.3 cc. 10^{-6} dilution intraperitoneally.
Treatment: Subcutaneously.

TABLE 6

INFLUENCE OF BORRELIDIN ON THE ANTI-TYPHOID ACTIVITY OF PENICILLIN G

Strain	*Penicillin mg./kg.*	*Average percentage of survivors Borrelidin mg./kg. 0*	*0.003–0.03*	*0.17*	*0.3–2.0*
PC1–412	90	85	55	65	—
	60	52	53	6.6	—
	45	70	20	—	—
P58A	90	65	63	50.0	—
	75	40	10	—	—
	60	14	3	—	25
P58A (mucin)	60	70	60	—	47.5
	30	60	45	—	27.5

The same type of results was obtained with oral treatment of this infection.

Welch's studies on the enhancement effect in typhoid infections were of particular interest. Experiments were carried out with two techniques using the well-known P58 A strain of *Eberthella typhi* and with a strain that was kindly furnished us by Dr. Welch, PCI-412. Two different types of experiments were carried out using strain P58 A. One, similar to the technique used by Welch, was the injection of a large amount of *E. typhi*, namely, 0.4 ml. of a six-hour broth culture, while the other was the type of infection usually used in our laboratories, the injection of 0.5 ml. of a 10^{-6} dilution of an

overnight broth culture suspended in mucin. The infection with strain PCI-412 was that used by Welch and his co-workers.

As can be seen from TABLE 6, no enhancement effect was observed. In fact, doses which show a higher ratio of borrelidin to penicillin seem to interfere to a certain degree with penicillin G.

The final experimental model to be presented here is the experiment with *Salmonella schottmuelleri* as shown in TABLE 7. Here, once again, no enhancement of penicillin G by borrelidin is observed.

In conclusion, it might be of interest to you to summarize the properties of enhancement of penicillin G by borrelidin and the enhancement factors investigated by different authors. This is done in TABLE 1. This table shows that borrelidin exhibits an enhancement of crystalline penicillin G, or at least a trend toward enhancement, in five of the seven experiments listed. It had no influence on *Eberthella typhi* or *Diplococcus pneumoniae* infections of mice if combined with penicillin G. Since it is not known whether the previously investigated enhancement factors could display other properties than those discussed in the literature, it is not possible to decide whether borrelidin is or is not identical with any of them. Furthermore, borrelidin is a pure compound identifiable by at least two specific biological properties, the *in vitro* effect on *Sarcina lutea* and the antiborrelia effect *in vivo*. No information is available to us at the present moment as to similar properties of other factors.

TABLE 7

ACTIVITY OF PENICILLIN G WITH AND WITHOUT BORRELIDIN. EXPERIMENTAL INFECTIONS WITH *Salmonella schottmuelleri*

Penicillin G mg./kg.	*Borrelidin mg./kg.* 0	0.033	0.066	0.132
120	8/10	8/10	10/10	—
66	16/30	10/20	20/30	3/10
45	3/10	1/10	3/10	2/10
30	1/10	—	0/10	—

Controls: 0/50.
Infection: 0.5 cc. 10^{-7} dilution of broth culture.
Treatment: 1 × subcutaneously.

Summary. Borrelidin was found to exhibit an enhancement effect on penicillin G in experimental infections with beta-hemolytic streptococci and meningococcus endotoxin. This influence seemed to be dependent on the dose of penicillin as well as on the borrelidin dose when a combination was administered by the parenteral or oral route. Very high doses of borrelidin seemed to interfere with the activity of penicillin. No enhancement effect of borrelidin was observed in infections with *Diplococcus pneumoniae*, *Eberthella typhi*, or *Salmonella schottmuelleri*.

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SECTION OF PSYCHOLOGY

THE Q-TECHNIQUE STUDY OF PERSONALITY

By WILLIAM STEPHENSON*

The study of personality seems, like Gaul, to be divided into three parts. One is concerned with literary and metaphysical or philosophical descriptions and analyses. Another is called, by some, *clinical* psychology. To the third, is given the name factorial analyses. Novelists are usually eminent in the first region, although some psychoanalysts do as well or better. Amongst many others, the standpoint of Gordon Allport,[1] with its *idiographic* trend, fits well into the second region. The early work of the Spearman School in London, with more recent excursions by Sir C. Burt,[2] his assistant Dr. Banks,[3] and Professor R. B. Cattell,[4] are, of course, examples of the third. The present paper begins a process of looking behind all three regions to study certain logical identities. Everyone knows, for example, that factorial analysis is rooted in statistical theorems. Few, however, would say that *les chiffres* count for much in clinical psychology, where insight is supposed to take their place. Amongst novelists, of course, the preoccupation with numbers is merely mercenary. Yet, I think it can be shown that, whereas the factorial analyst used numbers explicitly and objectively, the clinicians and novelists use them only implicitly and subjectively, although their thinking involves the selfsame procedure. In any case, it is certain that what the novelists and idiographists think about personality can be represented in statistical terms with considerable verisimilitude, if not precision, and that the ordinary methods of factorial analysis can be applied to these representations.

That this is the case was shown first, I think, in the application of Q-technique to Jung's great essay on *Psychological Types*,[5] which is a mixture of literary and clinical regards. Previous systematic study of introversion-extraversion had been in terms of individual differences, with disappointing results, whereas, what was required as a beginning was merely the direct representation of personalities to determine their similarities. Jung made use of some 2,000 traits to describe the introversion and extraversion features of personality. In Q-technique, these are defined as a *trait-universe*, from which samples may be drawn at random. Any personality can then be represented in terms of the sample, by giving high scores for traits which characterize it, and low for those which do not do so. If we assume that, for such a random sample, the *mean* score for the sample of traits will not differ much from personality to personality, and that the scores given to the large sample of traits will tend to be normally distributed, the conditions at once exist for the reduction of the data to standard scores, and for applications of the product-moment correlation coefficient. Different personalities can be correlated in terms of the sample of traits, and sets of such correlations can be factorized. I have already reported several brief studies of Jung typology carried out in such terms.[6, 7] It is sufficient to say that any of Jung's hypotheses can now be tested in a direct scientific manner, and that this was never achieved in terms of R-technique studies, that is, by way of the study of individual differences for samples of *persons* drawn from any defined population or universe of persons.

Similarly, it is possible to take a book of clinical case studies, such as Beck's[8] descriptions of personalities tested by the Rorschach method, and to reduce the literary compilations of details to a trait-universe of Rorschachian terms. Again, this universe can be sampled and personalities described in terms of the sample or samples, and these can be correlated. Some hundreds of pages of descriptions can be reduced, in this way, to the compass of a single correlation table, with as many variables in it as there are cases in Beck's book.

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Shorthand statistical descriptions of this kind, however, are merely a beginning. Its consequence is that hypotheses can be stated, tested, and proved or disproved in scientific fashion. I have already described a number of studies of this kind in Q-technique. In one, for example, two trait universes were defined, one consisting of 800 everyday terms that I found myself using in giving accounts of personalities to business executives in language which they could understand, and another a universe of 500 Rorschachian terms, taken from the aforementioned book of Beck's.[8] Samples of 400 were drawn from the former at random, and 120 from the latter. Ten men were then represented in such a way as to afford what I believe to be the first systematic attempt to offer some proof or disproof of Allport's hypothesis of functional autonomy.[1] For it was argued that, if for these men working with Rorschach traits of a presumably fundamental or underlying nature, the same factor patterns result for descriptions by the psychologist, as those by a number of naive subjects working with the everyday language traits, then by so much is functional autonomy *not* proven. Evidence pointed to the latter conclusion, of course only with reference to the Rorschach test conditions. The main point, however, is not that I want to argue for or against such a hypothesis at present. It is merely a reminder that a technique now exists for putting hypotheses such as Allport's to crucial tests.

In a general way, too, it is worth noting that different trait-universes may be held to represent different psychological or behavioral field conditions.[7] Thus, the language we use to describe personality to business men is quite different from that we would employ in reporting about nurses to a matron. We implicitly couch our terms to suit the circumstances. It is now possible, therefore, to study people in different circumstances by factor methods: the business man at work, at play, at home, with the appropriate trait-universes involved in each case.

But, on the same grounds, systematic *typology* may be said to have its roots in this same technique. Chein,[9] for example, like many others, argues that what is really involved in personality is the search for "enduring or persistent motives" which account for the intransigence of traits in different field conditions. The aforementioned Rorschach study had such a basis to it: that of more fundamental or persistent traits, which underlie the everyday descriptions we offer of a personality. In fact, typology, in general, can be conceived as systems of trait universes, one above another, with the more fundamental ones below.[7]

Again, the preoccupation of Guttman[10] and others in the search for "homogeneous" or "pure" tests and the like is psychometrically based in this same technique, as Loevinger[11] is perhaps noticing.

Finally, by way of preamble, Q-technique can be applied to mere handfuls of persons. Indeed, if need be, only *one* person could be studied, and large tables of correlations provided about him. There is nothing unusual in this. But an important possibility exists that factors determined for a few persons only, as few as half-a-dozen persons perhaps, can provide all the evidence one requires to prove or disprove psychological hypotheses, or to indicate what is *necessarily* and *alone* possible, even if hundreds of persons were tested instead. This, and the attendant practical facility of being able to apply factor devices with great precision to one or a few persons only, mark out the technique as a tool *par excellence* for clinical studies.

These various applications, and the assertions they involve, follow from the fact that, whereas earlier work had its *systematic* foundations laid in the definition of universes of persons, which could be sampled so that individual differences were adumbrated, Q-technique works, instead, with a far more available and amenable domain of universes, namely, those of traits or other particularities. These, as I have shown, can be handled systematically, just as can be universes of people; and the traits can be quantified with respect to many current per-

sonality concepts, such as "characteristicalness" of a trait in a personality, "idealisation," "projection," "rationalization," and the like.[6] But when a sample of traits is so quantified, as I have said, the *mean* score for all persons is the same. There are no individual differences in this regard. Thus, I find that I can reasonably represent the personalities of university students in terms of a sample of 210 traits drawn from Cattell's enquiries,[4] in such a way that their means are the same for all students, and their standard deviations too. Students can do the same for themselves just as readily. This can be done for the simple reason that there are as many statements of a positive nature in the trait-universe, or in the sample, as there are negative ones. For an item of the kind "trustworthy," there is always another such as "disloyal." If the one is given a high mark in characterizing a personality, the other receives a low one. In short, the means for significance for a large enough sample of traits will tend to be the same for all persons. For systematic purposes, we reduce the standard deviations of such arrays, about each person, to standard terms. That is, the product-moment correlation coefficient is at once applicable to the data without in any way doing violence to it. If I seek to represent extreme personalities, however, such as that of a severely hysterical-depressive woman, the condition that the *means* are zero is still true, but wider dispersions may be required in order to do justice to the case.

The matter I have just referred to has some unexpected ramifications. In R-technique analysis of mental tests, the correlational approach is very pertinent, because the *means* or *averages* provided by tests, for a sample of persons, are in a way quite arbitrary matters. If any test is made longer, or shorter, its mean would ordinarily alter *pari passu*. Factorists, therefore, correlate such tests, and this, of course, is based upon standard scores, *i.e.*, the mean of any test is made 0, and its standard deviation 1.0. As I say, this is a wholly reasonable and sensible procedure. But the same does not necessarily apply to *traits* which are quantified with respect to individual differences, for now we can't, so to say, arbitrarily alter the length of a trait. Thus, when Burt and Cattell take separate traits, such as . . . "assiduous," "interested in persons of the opposite sex," *etc.*, and quantify these with respect to individual differences for assumed randomized conditions, it is a considerable assumption to suppose that, as a *first* approximation, the *means* in these cases must be 0, and the standard deviations 1.0. On the contrary, the first assumption is likely to be that the *means* will be *necessarily* vastly different. One merely has to ask 100 women to estimate (1) their assiduousness, (2) their interest in men, on a 10-point scale, to see that (1) gains about 5 points on the average, and (2), 9 or 10. If, then, one were to seek to study these traits at a grass root level, it is gratuitous to assume that these means should be reduced to 0 in each case, whatever one might say about their standard deviations. There is nothing logically necessary in the assumption, as there is for mental tests. Yet Cattell and Burt go ahead without a moment's pause to wonder whether this assumption is warranted. Burt, it is true, would say that a Q-technique approach to such traits is preferable,[2] but he makes no suggestion as to why this is so.

It may well be that in neglecting the differences in *means* between traits, as Burt and Cattell do, the very essence of matters is thrown away, like a baby with the bathwater. There is some evidence already, indeed, that this is the case. It comes from a study I have made recently of Professor R. B. Cattell's list of 35 conative traits, such as "suspicious," "anxious," "frank." These had been studied originally by Cattell as a matter of R-technique, and he has provided a table of correlations for these traits as variables, for a sample population of 230 women. Factorized by Thurstone procedures, some 18 factors were presumed to be isolated by Cattell and identified after 20 months of rotation and study. Dr. Banks[3] has recently refactored the same table, using

Burt's summation procedures, and, after a month of work, provides a different set of factors, involving in her case, with nice crystallographic exactness, one general factor, a bipolar whose parts, divided exactly in half, provide another bipolar, and each of these halves, divided in half again into eight smaller parts. This geometrical patterning corresponds, also, to basic and group factors with which many of us have become more familiar, namely: a general or "basic" factor of *emotional stability or instability* (spiteful, self-willed, attention-getting, *etc.*); a group or broad factor of "cheerfulness" (the euthymic qualities, talkative, sociable, cheerful, *etc.*); another group factor identified with *esthenic-asthenic* qualities (roughly extraverted or introverted traits, such as immature, fickle, boorish, frivolous) and eight smaller or "narrower" factors, identified as *paranoid*, *compulsive*, *anxiety*, *adolescent hysteria*, *dominating*, *impulsive*, *cordial*, and *facile*, respectively. Banks considers that these factors are structurally related, whereas Cattell's are not so. But this seems only to mean that a hierarchy of classes is involved, with a *summum genus*, subordinate genera, narrower species, and still narrower sub-species.

Now it happens that I have also re-factored the same Cattell table, using Spearman methods, and arrive, after three days of work, at four group factors (ignoring some details, much as did Banks in her analysis, since they are not material to the present argument). These four factors give a reasonably excellent fit. They correspond very approximately to Banks' factors I, VII, and III (for my first three factors respectively), but my fourth factor has no obvious counterpart in her table. My interpretation of the factors, however, is very different.

This follows from two or three considerations, and from the Q-technique study I have made of the same traits. First, however, we should note that, whereas, Cattell's analysis is rightly enough empirical, nothing in it suggests that the women might be subject to rationalizations, stereotypies, and the like disturbers of orderly self-appraisals. Similarly in Banks' study, nothing of the kind is considered or suspected. It may be, of course, that these effects are thrown away with the bath-water, *means* which are, as I have indicated, basic to R-technique. And, if this is the case, one might well say good riddance to them, especially, if what is left behind has the precision and nicety of the hierarchy of factors provided by Banks. It is with this matter in mind that I turned to a Q-technique study of these same traits.

Professor Cattell kindly provided me with a detailed list of the 35 traits, each of which is there described in short paragraphs which subsume a number of apparently comparable terms. Thus, "depressed, solemn," is described as . . . "earnest and solemn most of the time. Not easily moved to laughter. Seeming slow and depressed rather frequently." This short paragraph contains at least seven separable statements, as do each of the others more or less. It was, thus, possible to compose a trait-universe of some 600 items from Cattell's list. A sample of 210 was taken. These were printed on cards, which the subjects could handle in three sets of 70 at a time.

In one study, 17 college women were employed. They were told to represent their own personalities, in a general context, in terms of each set of cards, on a prearranged frequency distribution.[5] Meanwhile, I had clinically tested 12 of the women, and could form my own judgment about their temperamental qualities.* I could, therefore, represent each in turn on the same 210 traits, and so make possible the direct correlation of their self-appraisals with what I considered their personalities to be. In addition, I could add appraisals for four other women, all of university student type, with whom I have had a long acquaintanceship. One is my wife, and three others are friends my wife and I have had to handle over a period of years.

Several tables of correlations were put together. One contained the 17 students'

* I made use of brief tests of G and K factors, *fluency*, Rorschach and Thematic Apperception, and *perseveration* tests.

own appraisals, plus mine of the four other women. Another contained the 12 students for whom I was able to make appraisals following the clinical testing to which I had subjected them. I found that the twelve students self-assessments correlated with my own assessment of them by amounts 0.47, 0.46, 0.43, 0.29, 0.28, 0.24, 0.18, 0.15, 0.13, 0.11, and 0.08 respectively. Only the first six of these are significant (N = 210, SE = 0.07 approximately). In the other six cases, the women have either no insight into their temperaments, or else are reflecting standard stereotypies, wittingly or otherwise. A shy, timid, dull, and inhibited woman, for example, assessed herself as above all else, "highly imaginative," "sophisticated—has wide interests and knowledge, especially intellectual." A most impulsive, almost a typical psychopathic student, regarded herself as "dependable and realistic—emotion doesn't get in the way of her judgment." There was patent and obvious lack of insight in these cases.

The appraisals upon which Cattell based his table, however, are not likely to involve such obvious crudities as these, since his were made by *other* students about their fellows in turn. Nevertheless, if, as a presumed expert, I cannot reach better agreement with the 12 women than the above would indicate, it is reasonable to wonder how much real insight students have in general about either their own, or other's, temperamental qualities. The suspicion becomes stronger when a Q-technique analysis is made of the tables of correlations for these students amongst each other as variables. For now, of four factors, in terms of which the correlations may be accounted, two are most reasonably interpreted as stereotyped notions of what women students would *like* to think they are, rather than an account of such matters as general stability of personality (Banks's and Burt's factor of general emotionality).

In short, there is considerable evidence of stereotypy in women's responses as soon as data of this kind are looked at by Q-technique procedures. Of four factors, for example, there was agreement between the women and myself in only one case. Considerable caution is needed, therefore, in the interpretation of factors issuing from R-technique, as has long been suspected.

I have to suggest, as a result of this and other studies, that there is nothing necessarily *basic* about the R-technique study of traits, since it throws away the most obvious information about them at the outset, namely, the differences in *means* (as a matter of individual differences). Q-technique does no violence of this order to the facts. Indeed, it leaves the facts untouched, except in so far as the assumption is made of equalized dispersions.

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SECTION OF ANTHROPOLOGY

THE CONCEPT OF LAND TENURE IN WORLD CULTURE

By JOHN M. COOPER*

Divergences between the thousand and one land tenure systems of the world are legion. But underneath the divergences are certain fundamental uniformities of dynamic, structure, and function, uniformities often masked by our divergent legal and anthropological terminologies. The present paper is an attempt to analyze and formulate some of the more important of these uniformities.

The land claims with which we are here concerned are claims to exclusive possession and occupation of a given area of the earth's surface, and to the exclusive exploitation and enjoyment of the area's resources and facilities. Where such exclusive rights of possession, occupation, and use are claimed by an integral autonomous political entity,—a band, tribe, nation, and so forth—as against alien entities, we have territorial sovereignty. Where they are claimed by individuals or by fractional groups—families, kinships, sibs, associations and so forth—within a given integral political entity, as against other individuals or fractional groups therein, we have land tenure.

Both territorial sovereignty and land tenure are found in practically all autonomous political entities—in all, if we interpret the terms leniently. Where, however, as occurs here and there, especially among some marginal peoples, a single conjugal family, or a very small group composed wholly or almost wholly of close kin, is, for all practical purposes, an autonomous political entity subordinate and beholden to no other such entity, it is merely a matter of words as to whether the land claims of such atomistic groups constitute territorial sovereignty or land tenure. In the strict sense of these terms, such a group would have territorial sovereignty, but not land tenure.

So much for definitions. We turn now to the uniformities. And first, all systems of land tenure, as regards both their uniformities and their divergences, are conditioned by and have their dynamic in the interplay of three sets of factors: psychological, social, and ecological.

The psychological factors are of both the conative and the cognitive order. Those of the conative order are, of course, the biological drives, particularly, but not solely, that of hunger, and the social ones, in so far as land-linked resources and facilities satisfy these desires. Tenure of land, as "exclusive," leaves the actual holder free to exploit the land without interference from others, and as "tenure," gives him security to hold it for a shorter or longer period. Psychological factors of the cognitive order are traditional or newly acquired techniques and skills for efficiently exploiting land-linked resources.

The social factors are the prevalent conceptions of self and of "one's own" for whom desire-fulfilment is wished. The conception of "one's own" will, of course, differ from one integral political entity to another, from one fractional group to another, and from individual to individual, depending, among other things, upon the solidarity, composition, and value-systems of the respective exploiters and holders.

The ecological factors are the land-linked resources and facilities recognized as capable, under use of known means, of satisfying the wants of the individual and of "his own." These land-linked resources and facilities comprise both tangible and intangible "goods." Among the more important land-linked tangible goods are: food, soil and surface for agricultural and pastoral production, clothing, light and fire, shelter, medicine, and manufactures. Among the more important land-linked intangible goods are: freedom of movement and transit, privacy, defence, recreation, es-

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thetic enjoyment, prestige, power, sentimental attachments, "at-homeness," familiarity (important also for exploiting resources), religious loyalties and associations.

These three sets of factors constitute the dynamic uniformity, it would seem, back of all systems of land tenure. This is the first uniformity, a fairly obvious one, to which attention is here given. To the second, that of selectiveness, we now turn.

Each culture, or each autonomous political entity or politically independent society of men living under a given culture, carries out in its land-tenure system a twofold selective process.

First, each such entity or society selects, in accordance with its specific desires and social organization, some resources and facilities for exploitation and enjoyment, and neglects others from among the almost numberless available tangible and intangible resources and facilities linked to the land it claims under territorial sovereignty. For example, a given non-literate people may thus neglect the mineral fuels under or on the surface of the land, whereas, to us Occidentals of the twentieth century, these resources may be the most valued land-linked goods in a given area. The divergence in this respect of selection between the land tenure systems of the world, as between our own Occidental ones and those of other peoples, is one, so to speak, not of kind, but of number and degree. Each system both selects and neglects. Our own modern American one, for example, differs from others, especially those of many non-literate ones, in selecting a greater number of resources and facilities and in neglecting fewer.

Second, from among the land-linked resources and facilities, tangible and intangible, actually selected for exploitation and enjoyment, each autonomous political entity reserves at least some for free non-exclusive exploitation and enjoyment by all its constituent individuals and fractional groups. Some entities reserve practically all, and then we have land tenure systems that are nearly 100 per cent communal. But no political entity, neither our own nor any other to our knowledge, at any level of technological achievement, turns over all its land-linked resources and facilities to its constituent individuals and fractional groups for their respective exclusive exploitation and enjoyment. In brief, in no political entity is the land tenure system 100 per cent private. Some systems have more of communal tenure, some more of private tenure, and these may be spoken of, respectively, as communally oriented or privately oriented. But the difference between the systems or between, for instance, our own system and those of non-literate peoples, is one of degree and proportion, rather than of kind. Between the most extreme private orientation, as in our own modern American system, and the most extreme communal one, as, for instance, in certain Plains and Great Basin tribes, occur myriad intermediate gradations, intermediate mixtures in various proportions of the private and the communal elements. All land systems are alike and uniform in so far as they are blends of both private and communal elements.

We now come to our third uniformity, that of limitations. Even where the integral political entity turns over part of its land or the use thereof to individuals or fractional groups, it does so under limitations and restrictions. It makes reservations. These limitations, restrictions, and reservations concern firmness and duration of tenure, and freedom to exploit, enjoy, and alienate.

Among non-literate peoples, these limitations and restrictions are many, differing, as is well known, from people to people, but are a phenomenon common to all such peoples. Some of the more common limitations are: "ownership" amounting to little more than "usufruct"; tenure only during occupation or use; absence of right or, at least, custom of sale; use, exploitation, and enjoyment restricted to a very few specific land-linked resources and facilities.

Our own modern American tenure in fee simple, one of the least restricted forms of land tenure, perhaps the least restricted, in

the career of human culture, is nevertheless cabined, cribbed, and confined in scores of ways. To list only a few of these limitations, restrictions, and reservations: the power of eminent domain; the police power, which may enforce, *e.g.*, laws of zoning and nuisance abatement; the taxing power, which may demand high inheritance taxes on landed estates or perhaps even capital levies thereon; rights of transit across owned land, and similar easements; public rights of use of navigable streams running through privately owned land; air rights across owned land; certain limitations on subsoil rights; limitations on freedom of bequeathment; spendthrift trusts; and so forth. Further, estates in fee tail are still recognized in six of our states. Also, apart from enacted law, what may fairly be called customary law, enforced, not by courts, but by public opinion, brings strong pressure to bear upon certain classes of land holders against misuse of their land or against alienation thereof to other than the holders' offspring or near kin; and, since a year ago unenforceable at law, yet still widely prevalent in many large sections of our country, are restrictive convenants held in force by extralegal local sentiment and approval.

Limitations, restrictions, and reservations, as regards both private ownership and private rights of alienation and use, are consistently recurring phenomena, characteristic, it seems, of all systems of land tenure known to us. Where such limitations go far, whether in non-literate political entities or, for example, in pre-war Nazi Germany, such private tenure as obtains may be called indifferently either "ownership" or "usufruct." In few systems can a sharp line be drawn. We as anthropologists would probably do well, in the interests of clarity, to scrap both terms and keep to the neutral one, "tenure."

A fourth uniformity, the last to be dealt with, is the notion, implicit or explicit, of trusteeship that appears, we believe, in all land tenure systems.

Explicit recognition of such trusteeship is a commonplace in non-literate societies, as, *e.g.*, in the numerous cases where the integral political entity's land is vested in the chief or tribal council to be held in trust for the people and to be administered for and distributed to them as need arises, or, where land owned by an individual or by a fractional group must, by customary law, be held in trust for the individual's descendants or heirs, or for present and future members of the group.

The notion of trusteeship is likewise present, in part implicitly and in part explicitly, in our own Occidental system of land tenure, including our modern American one. It is at least implicitly present in the power of eminent domain, in the police power, and in many of the limitations, such as some estates in fee tail, which we have listed. It is explicit in the Christian tradition of property, including landed property, as a stewardship or trusteeship. Under this tradition, an historic component of our Occidental culture and operating mostly on a non-legalistic level, surplus goods and property, that is, such as are not needed to meet the legitimate wants of the owner, must be shared with "the poor," those who need, but lack such resources and facilities required for a decent standard of living.

To sum up the present brief paper, we have attempted to analyze and formulate four of the basic uniformities in the concepts of land tenure which prevail in the cultures of the world. These four uniformities are:

(1) A triple dynamic—psychological, social, and ecological—lies back of all systems of land tenure.

(2) Each system works under a double selective process: (a) selecting some land-linked resources and facilities for exploitation and enjoyment, and neglecting others; and (b) of those resources and facilities chosen, selecting some for free use by all members of the political entity, and permitting exclusive tenure and use of others to individuals and fractional groups.

(3) Where exclusive tenure and use are granted to individuals and fractional groups, limitations and restrictions of many kinds are imposed upon such tenure and use, the

political entity reserving much for the benefit of other individuals or fractional groups.

(4) An explicit or implicit notion of trusteeship, on the part of the integral political entity and/or on the part of individuals and fractional groups, is extremely widespread in land tenure systems and is probably present in all of them.

SECTION OF PHYSICS AND CHEMISTRY

PRECISION COLORIMETRY

By C. F. HISKEY*

There have been two general ways by which the precision of colorimetric analyses has been improved. One of these utilized the design of sensitive photoelectric circuits capable of detecting as little as 0.00001 of the optical scales. This has been done by such workers as Von Halban, Kortüm, Rabinowitch, and Klotz and Dole. The other approach involved a detailed investigation of the errors of transmission measurements, so that these being understood, they then could be minimized. This method is associated with the names of Von Halban, Twyman and Lothian, Kortüm, Ringbom, and Hamilton. From these workers, our present approach to the measurement of the relative transmittance of a solution has been derived.

In general, however, their colorimetric procedures involved a comparison of a solvent with a solution. The measurement of relative concentrations, which requires a measurement of a transmission ratio, has not been extensively investigated. Such is the purpose of this study.

The Transmission Ratio. Consider a situation where three beams of light, of identical frequency and intensity, are permitted to fall on three identical absorption cells which contain, respectively, pure solvent, colored solution of concentration C_1, and colored solution of concentration C_2 (Figure 1).

A comparison of the various exit light intensities of the solutions with that of the pure solvent, would give the following relations;

$$I_1 = I_0 e^{-kC_1 l}; \; I_2 = I_0 e^{-kC_2 l}. \qquad (1)$$

These are, of course, the Beer-Lambert expressions for those situations where comparison is made against the solvent being used.

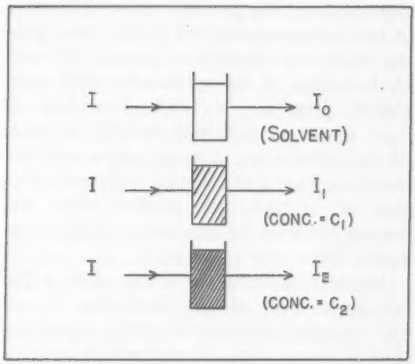

Figure 1

The ratio of the light intensities leaving the solutions of concentrations C_2 and C_1 would be:

$$\frac{I_2}{I_1} = \frac{I_0 e^{-kC_2 l}}{I_0 e^{-kC_1 l}} = e^{-kl(C_2 - C_1)} = e^{-kl(\Delta C)}. \qquad (2)$$

This will be termed the transmission ratio. It is apparent that it is the concentration difference between the two solutions which determines the value of I_2/I_1.

If the concentration difference now is expressed in terms of the concentration ratio α, *i.e.*, C_2/C_1, the following expressions

* Division of Analytical Chemistry, Polytechnic Institute of Brooklyn, Brooklyn 2, N. Y. This paper, illustrated with lantern slides, was presented at a meeting of the Section on March 1, 1949.

apply:

$$\frac{C_2}{C_1} = \frac{C_1 + \Delta C}{C_1} = \alpha, \qquad (3)$$

also

$$\Delta C = C_1(\alpha - 1) = C_2\left(\frac{\alpha - 1}{\alpha}\right)$$

$$I_2/I_1 = e^{-k1C_1(\alpha-1)} = e^{-E_1(\alpha-1)}. \qquad (4)$$

EQUATION 4 indicates the relationship which would prevail if the transmission of the solution under analysis was measured by comparison against a solution of the same substance whose concentration was known. This is different from ordinary colorimetric practice. It requires that a standard solution be placed in one cell of a null type colorimeter, with the light intensity adjusted to give full scale deflection of the galvanometer, and in the other cell, the unknown solution is placed, followed by balancing of the system by what ever circuit principle is used. Providing a light source of sufficient stability is part of the colorimeter, a single photo cell instrument may also be used with substitution of the unknown solution after the instrument is set for maximum deflection by means of the color standard.

From an examination of EQUATION 4 the important role of the extinction E_1 of the standard solution becomes apparent. This is demonstrated in the plot of I_2/I_1 *vs.* E_1 given in FIGURE 2. The plots are made for different values of the concentration ratio α.

It is evident that with increasing extinction in the reference standard the transmission ratio becomes increasingly sensitive to the ratio of the concentrations being compared. Even when α is only 1.01, it is still possible to demonstrate that fact without much difficulty by working with a reference standard whose extinction is somewhat more than unity. For a standard whose extinction is 4.0, I_2/I_1 would be equal to 0.96, and if the colorimeter scale could be read to 0.005, then a ratio as low as 1.0012 ought to be detectable.

It will next be useful to compare the precision of measurement in ordinary colorimetry with that of the transmission ratio function. In this way, it will be possible to ascertain the conditions requisite for increased precision.

Precision of Transmission Ratio Measurements. The error functions of interest are those involving the ratio of C_2/C. It may be shown that:

$$\frac{d(\alpha - 1)}{(\alpha - 1)} = \frac{d(\Delta C)}{C}; \qquad (5)$$

$$\frac{d\alpha}{\alpha} = \frac{d(\alpha - 1)}{\alpha} = \frac{dC_2}{C_2}. \qquad (6)$$

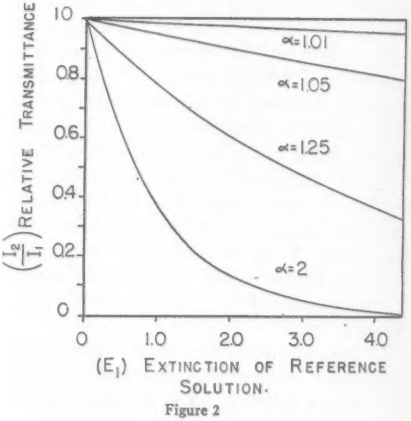

Figure 2

By deriving the error functions in terms of I_2/I_1 expressions (7) and (8) may be obtained.

$$\frac{d(\Delta C)}{\Delta C} = \frac{d(I_2/I_1)}{I_2/I_1 \ln I_2/I_1}. \qquad (7)$$

$$\frac{dC_2}{C_2} = \frac{d(I_2/I_1)}{\frac{I_2}{I_1}\left(\ln \frac{I_2}{I_1} + \ln \frac{I_1}{I_0}\right)}. \qquad (8)$$

The value of these error functions may be approximated by substituting small finite increments for the infinitesimals. $\Delta (I_2/I_1)$ is the uncertainty of reading the exact value of the transmission ratio on the colorimeter

scale. It arises from the fact that the setting at some value of the transmission ratio is always uncertain by a constant quantity, which in most commercial instruments will be of the order of 0.01 to 0.002 of the total scale. $\Delta (I_2/I_1)$ is, therefore, a constant quantity for any particular colorimeter being used. It may be evaluated experimentally by taking a standard and an unknown, and measuring the transmission ratio repeatedly. Each measurement should include the operations of emptying, refilling, and repositioning the cuvettes. $\Delta(I_2/I_1)$ may be taken as twice the value of the average deviation.

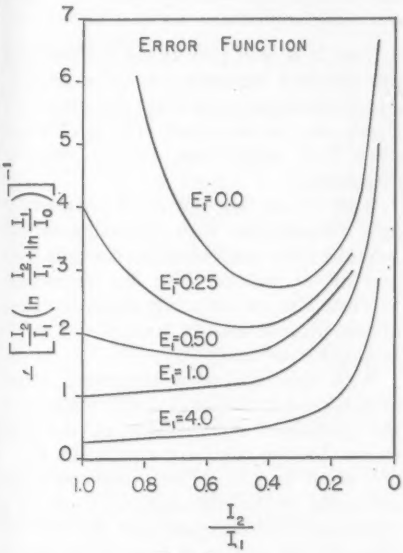

Figure 3

In FIGURE 3, a plot of the reciprocal of $I_2/I_1 \ln I_2/I_1$ is given as a function of the transmission ratio. The curve marked $E_1 = 0.0$ is the only one under consideration. The value of $\Delta I_2/I_1$ is left unspecified. Here it can be seen that the relative error is infinite for 0.0 and 100 per cent transmission ratios. At intermediate values, the relative error decreases to a minimum and then rises again. In the region between 20 and 65 per cent, the curve is nearly flat and, hence, a minimum and nearly constant error is achieved by working in this region.

Differentiating the expression with respect to I_2/I_1 and setting the function equal to zero gives the point of minimum error which is found to correspond to a value of 0.368. The numerical values of $d(\Delta C)/\Delta C$ can be shown to be equal to those of dc/C when the concentration is determined by ordinary colorimetric methods. In other words, the determination of a concentration difference is no more precise than is the determination of a concentration by comparison against the solvent.

In chemical analysis, however, the prime interest is in the value of the total concentration and, therefore, the main concern is with the error involved in that measurement. This error is seen (from an inspection of EQUATION 8 and the graphical plots in FIGURE 3) to be dependent in a pronounced manner on the value of the extinction of the comparison standard.

In these graphs, also, only the reciprocal of $I_2/I_1(\ln I_2/I_1 + \ln I_1/I_0)$ is plotted on the ordinate instead of dC_2/C_2. In this way, the graph is generalized to cover all photoelectric colorimeters, since the value of the term $\Delta (I_2/I_1)$ is not specified. Curves are given for a number of values of the extinction of the standard solution, *i.e.*, $E_1 = 0.25, 0.50, 1.0$ and 4.0.

Now it is seen that as soon as the value of E_1 exceeds zero the value of the relative error becomes finite at the 100 per cent end of the colorimeter scale. At all other values of the scale, the error for any given extinction of the standard is less than is the case with solvent comparison. As the value of the transmission ratio approaches zero, the entire group of curves approach infinity. Therefore, little gain in precision is to be expected in that region of the scale. Fortunately, that region need not be used in any analytical operation. However, in the 100 per cent region, the decrease in error is extremely rapid with increasing extinction of the standard. In FIGURE 4,

a plot (solid line) is given for the error involved in measuring the concentration of an unknown when its concentration is identical with that of the standard. This plot is made as a function of the per cent transmission of the standard.

Here, it can be seen how rapidly the error declines as the extinction increases. When the standard has a transmission of as much as 0.69, the relative error of making this particular measurement is identical with minimum error achieved in ordinary colorimetry, and, for the other values of I_2/I_1 at the same transmission for the

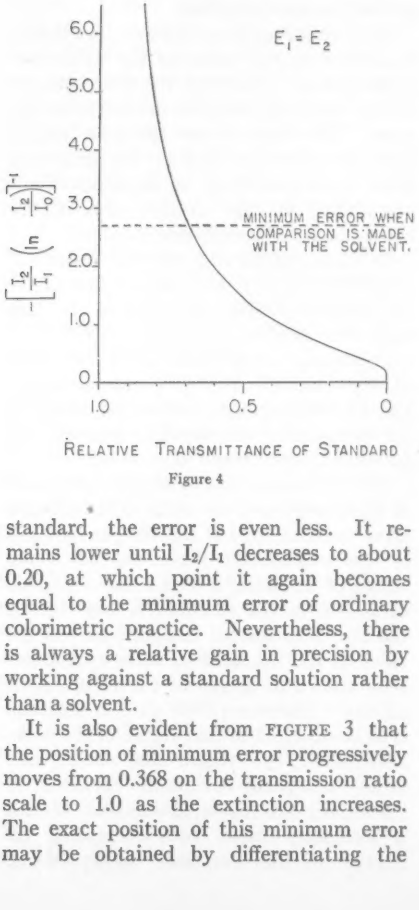

Figure 4

standard, the error is even less. It remains lower until I_2/I_1 decreases to about 0.20, at which point it again becomes equal to the minimum error of ordinary colorimetric practice. Nevertheless, there is always a relative gain in precision by working against a standard solution rather than a solvent.

It is also evident from FIGURE 3 that the position of minimum error progressively moves from 0.368 on the transmission ratio scale to 1.0 as the extinction increases. The exact position of this minimum error may be obtained by differentiating the function with respect to I_2/I_1 and setting it equal to zero. When this is done,

$$\ln \frac{I_2}{I_1} + \ln \frac{I_1}{I_0} + 1 = 0;$$

also

$$\ln \frac{I_2}{I_1} + 1 = 0$$

and

$$\frac{I_2}{I_1} = e^{-(1-E_1)}. \qquad (10)$$

Here, it is seen that as the extinction of the standard increases the value of I_2/I_1 steadily increases, and when the extinction equals one, the minimum error is obtained when I_2/I_1 equals one, *i.e.*, at identical extinctions.

Were it not for the rapid decrease in light transmission with increasing extinction, the error could be reduced at will. In practice, it will probably be impractical to work with an extinction much in excess of four, because the light transmission would be only 1.8 per cent.

With this limitation recognized, however, a considerable gain is still achieved in the precision. Examination of the plot shows that the minimum error when $E_1 = 0$ is equal to 2.72. This occurs when the extinction of the unknown is 1.0 or has a transmission of 36.8 per cent. In the case where E_1 has a value of four, the minimum error is 0.25, or about one eleventh that obtained with the solvent as the comparison standard. In this case, however, the extinctions of the unknown and the standard must be made nearly equal to achieve the precision gain.

This general treatment of error applies only to those cases where the Beer-Lambert relation holds and where the chemical operations have greater precision than those of the colorimetric measurements. In practice, of course, solutions of high extinction may often be of relatively high concentration. In such cases, deviations

from the Beer-Lambert expression may become apparent.*

Application of the Transmission Ratio Method. The utility of the transmission ratio method of colorimetry may be demonstrated from the published work of Kortüm and Bastian. In a series of measurements of the extinction coefficient of 2,4 dinitrophenol solutions, Kortüm observed that greater precision could be obtained in determining concentrations by making a comparison of an unknown with a standard than could be obtained in an absolute measurement of the extinction. His data in part are listed in Table 1.

TABLE 1

COMPARISON OF THE TWO METHODS OF COLORIMETRY ON 2,4 DINITROPHENOL.

	I_1/I_0	I_2/I_0	$E_2 = \log_{10} I_0/I_2$	C_2 Din. by transmission Ratio Method
First day				
	.37072	.36214	.44112	4.982×10^{-5}
	.37100	.36254	.44064	4.980
	.37114	.36280	.44033	4.979
Average	.37095	.36249	.44139	
	±.00016	±.00024	±.00028	
Second day				
	.36940	.36108	.44239	4.979
	.36968	.36130	.44213	4.980
	.36994	.36164	.44172	4.979
Average	.36967	.36134	.44208	4.980 } Av. of all 6
	±.00018	±.00020	±.00024	±.001 }

If the average deviations from each of the four sets of transmission data are averaged, it will be found that $\Delta I/I_0 = \pm.00020$. The values of $\frac{\Delta E_2}{E_2}$, on the ordinary colorimetric basis, and the $\frac{\Delta C}{C_2}$, by the transmission ratio method, now may be calculated and found to be ±.00055 and ±.00020, respectively. The observed values averaged for the two sets of extinction and concentration values are ±.00059 and ±.00020, respectively. These are seen to be in good agreement with the experimental evidence.

It will be observed, however, that between the transmission data of the two days there is an absolute shift of about 0.0012, due perhaps to some alteration in the optical or electrical circuit. This creates a large spread in the values for E_2, but is virtually without effect on the value of C_2 determined by the transmission ratio. Thus, in another way, the advantages of this method are demonstrated.

More recently, Bastian applied the transmission ratio method to the determination of copper in various copper base alloys. The instrument used by him was the Beckman spectrophotometer (Model Du). In this instrument, the optical scale may be extended by opening the slits so that a larger section of the spectrum is passed through the absorption cell. Working with solutions whose extinctions were about 2.5, he was able to make analyses of copper in lead brasses, phosphor bronzes, and synthetically prepared unknowns with a precision of ±.001 and ±.002. There is evidence in this work that the limits of precision are determined, not by the colorimetric measurements, but, rather, by the chemical operations. Nevertheless, the precision of his work, as well as the accuracy, (assuming the electrolytic values to be correct, the agreement obtained colorimetrically was always within one to two parts per thousand), far surpasses any other colorimetric process previously reported.

* A treatment of the error function when the system deviates from the Beer-Lambert equation has been made. It will appear shortly, along with a consideration of refractive index and density changes in the solutions.

In a future publication, data on the performance of a number of commercial photoelectric colorimeters will be published. In a preliminary way, it may be said that tests on solutions of a number of salts, *i.e.*, potassium dichromate, copper sulfate, and on various dyes confirm the utility of this approach.

Method as Applied in Commercial Colorimeters. To apply the above principle to commercial photo electric colorimeters or spectrophotometers, it is a requisite condition that the instrument used must have a variable optical scale. This variation is achieved in practice in a number of different ways. One method is that of adjusting the slits on a monochromator so that a larger fraction of the spectrum is passed through the solution. A second, is to vary the current passing through the light source and thus increase the emission intensity. A third method is to operate the indicating device, *i.e.*, galvanometer, *etc.*, with a variable sensitivity. Thus, if only a fraction of the total current is fed to a galvanometer during measurements on solutions of low extinction, then when the shift is made to higher extinctions, the shunt may be adjusted to pass an increasing fraction of the photo current through the galvanometer and, thus, effectively increase the optical scale.

The transmission ratio measurement is then made with a pair of optically matched cuvettes each containing one of the solutions to be compared. Placing the standard solution in the monochromatic (or at least filtered) light beam, adjustment of the optical scale is made until the instrument reads 100 per cent transmission. The analyst must then make sure, at this point, that the lower end of the scale is at zero. With the instrument now properly set, the second solution is placed in the light beam, whereupon, if its extinction is greater than that of the standard solution, the new value read will be some value less than 100. It will equal $100(I_2/I_1)$. Should the extinction of the second solution be less than that of the standard, the reading of the I_2/I_1 value will be off the scale, since it will be in excess of 100. To make the comparison then, it is necessary to reverse the order of the two cells.

There are several precautions to bear in mind in this type of colorimetry. In the first place, the optical characteristics of a pair of cuvettes must be known with a precision equal to the best precision anticipated for the work. This will involve comparing the cuvettes when they contain a solution of high, but identical, extinction in them. The extinction of the solution will obviously be the maximum for which full scale deflection can be achieved. Then, the following terms may be applied:

$$\frac{I_2}{I_1} = e^{-kcl_1(L-1)} \quad \text{where} \quad L = \frac{l_2}{l_1},$$

i.e., the ratio of the apparent path lengths in the two cells. This ratio, once evaluated, is then applied as a correction term to all other work. It, too, should be checked from time to time, since alterations of the surfaces of the optical flats will change L.

Next, it will be necessary to determine the extinction of the standard solution and to prepare a precise calibration curve for the purpose of seeing the agreement with the Beer-Lambert equation. This should be done in the following manner. Prepare a number of standard solutions covering the range of extinctions desired. If, for example, it is one's intention to work from 0.1 to 3.0, then a thirty-fold concentration range would be needed. Start with pure solvent in one cell and successively measure the transmissions (I_1/I_0) of the solutions until the value of I_1/I_0 has dropped to about 0.37. Then remove the solvent from the cuvette and substitute in it some of the solution which had the 0.37 value. Compare the two cuvettes to see if I_2/I_1 equals unity. If not, a preliminary value of L will thus be obtained.

Continue measuring I_2/I_1 values for the more concentrated solutions. Proceed in this way until the value of $I_2/I_1 \cong 0.37$. This means that the transmission of the solution being examined is only 0.135 with respect to the solvent, although it is 0.37

with respect to a solution whose own transmission is only 0.37. Again, L is evaluated by changing our standard so that it is identical with the one already in the other cuvette. Taking this as the second reference point, I_2/I_1 values may be measured for the more concentrated solutions. In this way, if the Beer-Lambert equation applies, the precision of measuring the slope relating E to C will be kept at the maximum value possible for the instrument and the extinction chosen.

When measurements for the entire concentration range which the instrument can handle have been made, the value of L will be finally evaluated, and with maximum precision, using the solution of highest concentration.

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CONFERENCES HELD

SECTION OF BIOLOGY

CONFERENCE ON "COCCIDIOSIS"

MARCH 4 AND 5, 1949

The Section of Biology held a Conference on "Coccidiosis." Doctor Sterling Brackett, American Cyanamid Company, Stamford, Connecticut, was the Conference Chairman in charge of the meeting.

The program consisted of the following papers:

Friday, March 4

Morning Session. Chairman, Norman R. Stoll.

"Introductory Remarks by the Conference Chairman," Sterling Brackett.

"Comments by the Honorary Chairman", E. E. Tyzzer, Harvard University, Cambridge, Mass.

"The Economic Losses Due to Coccidiosis," by A. O. Foster, Zoological Division, U.S.D.A., Beltsville, Maryland.

"Special Problems in Coccidiosis of Chickens in Different Regions of the United States,"—P. P. Levine, Moderator. A Round Table Discussion, by R. A. Bankowski, C. W. Barber, J. P. Delaplane, L. C. Grumbles, P. A. Hawkins, E. H. Peterson and K. C. Seeger.

"Some Factors Influencing the Origin and Course of Epidemics of Coccidiosis," by C. Horton-Smith, Animal Health Trust, Poultry Research Station, Houghton Grange, England.

"The Course of Coccidiosis Epidemics in Broilers in Delaware," by K. C. Seeger, University of Delaware, Field Station, Georgetown, Delaware.

"Effect of Litter Moisture on Outbreaks of Coccidiosis," by A. E. Tomhave, University of Delaware, Newark, Delaware.

"Laying House Coccidiosis Due Presumably to *Eimeria acervulina*," by E. H. Peterson, State College of Washington, Pullman, Wash.

Afternoon Session. Chairman, Elery R. Becker.

"Survival of *Eimeria acervulina*, *E. maxima* and *E. tenella* Oocysts Exposed on Soil under Various Field Conditions," by M. M. Farr and E. Wehr, Zoological

Division, U.S.D.A., Beltsville, Maryland.

"Some Host Parasite Relationships between *Eimeria tenella* and Chickens," by C. A. Herrick, C. A. Ripsom, C. A. Johnson, and J. W. Daugherty, University of Wisconsin, Madison, Wisconsin.

"Factors Involved in Tests for Acquired Immunity in *Eimeria tenella* Infections of the Chicken," by E. Waletzky and C. O. Hughes, American Cyanamid Company, Stamford, Conn.

"The Effect of the Protozoan Parasite, *Eimeria stiedae*, on the Succinic Dehydrogenase Activity of Liver Tissue of the Rabbit," by B. F. Smith, Spelman College, Atlanta, Georgia; and W. H. McShan, Department of Zoology, University of Wisconsin, Madison, Wisconsin.

"Coccidiosis as a Disease in Turkeys," by N. F. Morehouse, Doctor Salsbury's Laboratories, Charles City, Iowa.

"The Development of Naturally Acquired Coccidial Infections in Lambs," by J. S. Dunlap and P. A. Hawkins, Department of Bacteriology, Michigan State College, East Lansing, Michigan.

"Coccidiosis in Calves,"—A Moving Picture, by L. R. Davis, Regional Laboratory, U.S.D.A., Auburn, Alabama.

Saturday, March 5

Morning Session. Chairman, F. Y. Wiselogle

"The Relative Efficacy and Safety of New Drugs for Poultry Evaluated by Adequately Controlled Tests," by J. H. Collins, Veterinary Medical Section, F. D. A., Federal Security Agency, Washington, D. C.

"Qualitative and Quantitative Comparisons of Different Types of Anticoccidial Drugs in *Eimeria tenella* Infections of the Chicken," by E. Waletzky and C. O. Hughes, American Cyanamid Company, Stamford, Connecticut.

"Suppressive Activity of Bisphenols Against Cecal Coccidiosis (*Eimeria tenella*) in Chickens," by J. E. Johnson, R. D. Mussell, and A. J. Dietzler, Biochemical Research Laboratories, Dow Chemical Company, Midland, Michigan.

"Para-substituted Phenylarsonic Acids as Prophylactic Agents Against *Eimeria tenella* Infections," by F. C. Goble, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

"Nitrofurazone and Coccidiosis," by P. D. Harwood and D. I. Stunz, Dr. Hess and Clark, Ashland, Ohio.

"The Anticoccidial Activity of Nitrophenide," by E. Waletzky and C. O. Hughes, American Cyanamid Company, Stamford, Connecticut.

"Additional Information on the Use of Sulfaquinoxaline for the Control of Coccidiosis in Poultry," by L. C. Grumbles, Louisiana State University, Baton Rouge, Louisiana.

"Continuous Low Level Sulfaquinoxaline Feeding in the Practical Control of Coccidiosis in Broilers," by E. L. Jungherr and J. D. Winn, University of Connecticut, Storrs, Connecticut.

Afternoon Session. Chairman, P. P. Levine.

"Borax in the Control of Experimental *Eimeria tenella* Infection of Chickens," by E. E. Wehr, Zoological Division, Bureau of Animal Industry, Beltsville Research Center, Beltsville, Maryland.

"The Effect of Various Agents in the Treatment of Experimentally Induced Coccidiosis (*Eimeria tenella*) in Chickens," by K. C. Seeger, University of Delaware, Field Station, Georgetown, Delaware.

"The Chemotherapy of Coccidiosis Due to *Eimeria acervulina*," by E. H. Peterson, State College of Washington, Pullman, Washington.

"Growth and Mortality of Chickens as Affected by the Floor Litter," by D. C. Kennard and V. D. Chamberlin, Poultry Science Department, Ohio Agricultural Experiment Station, Wooster, Ohio.

"Preliminary Experiments with Sulfamethazine in Bovine Coccidiosis," by L. R. Davis and G. W. Bowman, Regional Laboratory, U.S.D.A., Auburn, Alabama.

"The Effect of Small Doses of Drugs on

the Oocyst Production of Infections with *Eimeria tenella*," by Sterling Brackett and A. Bliznick, American Cyanamid Company, Stamford, Connecticut.

"Consideration in the Practical Control of Intestinal Coccidiosis of Domestic Rabbits," by E. E. Lund, U. S. Rabbit Experiment Station, Fontana, California.

"Coccidiosis in Native California Valley Quail and Problems of Control," by C. M. Herman, California Division of Fish and Game, University of California, Berkeley, California.

SECTION OF PHYSICS AND CHEMISTRY

CONFERENCE ON "SPECIFIC METHODS OF ANALYSIS" MARCH 25 AND 26, 1949

The Section of Physics and Chemistry held a Conference on "Specific Methods of Analysisr" Doctor Samuel E. Q. Ashley, General Electric Company, Pittsfield, Massachusetts, was the Conference Chairman in charge of the meeting.

The program consisted of the following papers:

Friday, March 25

Morning Session. Chairman, Samuel E. Q. Ashley.

"Introductory Remarks by the Conference Chairman," Samuel E. Q. Ashley.

"X-ray Absorption and Chemical Analysis," by Hermann A. Liebhafsky, Research Laboratory, General Electric Company, Schenectady, N. Y.

"The Analytical Specificity of Counter Current Distribution," by J. Delafield Gregory and Lyman C. Craig, Rockefeller Institute for Medical Research, New York, N. Y.

"The Method and Application of Differential Thermal Analysis," by Ralph E. Grim, State Geological Survey Division, State of Illinois, Urbana, Illinois.

Afternoon Session. Chairman, Leland A. Wooten.

"Optical Properties of Surface Films," by Alexandre Rothen, Rockefeller Institute for Medical Research, New York, N. Y.

"Electrolytic Analysis of Tarnish Film on Metals," by Wilfred E. Campbell, Bell Telephone Laboratories, New York, N. Y.

"Measurement of Properties of Thin Films on Chromium by the Reflection of Polarized Light," by J. B. Bateman and Margaret W. Harris, Camp Detrick, Maryland.

"Goniometric Analysis of Crystals," by J. D. H. Donnay, The Johns Hopkins University, Baltimore, Maryland.

Saturday, March 26

Morning Session. Chairman, N. Howell Furman.

"Quantitative Analysis by Means of Catalytic Hydrogenation Reactions," by E. D. Dunlop, Experimental Station, E. I. duPont de Nemours and Company, Inc., Wilmington, Delaware.

"Analysis of Mixtures Based on Rates of Reaction," by Thomas S. Lee, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota.

"Automatic Paper Chromatography" by, Ralph H. Müller and Doris L. Clegg, Department of Chemistry, Washington Square College of Arts and Sciences, New York University, New York, N. Y.

NEW MEMBERS

Elected March 24, 1949

SUSTAINING MEMBERSHIP

Allen, Shannon C., Ph.D., Medical Physiology. Director, Aviation Research Unit, Cornell University Medical College, New York, N. Y.

Colowick, Sidney P., Ph.D., Intermediary Metabolism. Associate Professor of Biological Chemistry, University of Illinois, Chicago, Ill.

Dupre, Robert E., M.D., Geology, Mineralogy, Psychology. Private Practice of Medicine and Surgery, Ville Platte, Louisiana.

Finkelstein, Max I., B.A., Cultural Anthropology. Finkelstein Textile Co. Inc., New York, N. Y.

ACTIVE MEMBERSHIP

Adler, George, B.S., Chemistry. Student, Division of Graduate Studies, Brooklyn College, Brooklyn, New York.

Alexander, John Deaver, M.D., Renal Physiology. Fellow, Department of Medicine, New York University, New York, N. Y.

Andrews, C. W., Ph.D., Ichthyology. Instructor in Biology, Washington Square College, New York University, New York, N. Y.

Archawski, Wladimir V., Mechanics and Mechanics of Fluids. Chairman of the Board, Electronic Dusting Corporation, New York, N. Y.

Armistead, George C. Jr., M.D., Hematology. Instructor in Medicine, Cornell University School of Medicine, New York, N. Y.

Arons, Walter L., M.D., Endocrinology. Fellow in Medicine, Johns Hopkins Hospital, Baltimore, Maryland.

Barker, Samuel B., Ph.D., Physiology. Associate Professor, College of Medicine, University of Iowa, Iowa City, Iowa.

Barrett, Walter E., B.S., Pharmacology. Assistant Pharmacologist, Ciba Pharmaceutical Products, Inc., Summit, N. J.

Beaty, Annabel, B.S., Nutrition. In Charge, Nutrition Laboratory, National Dairy Research Laboratories, Inc., Oakdale, L. I., N. Y.

Beck, Gustav J., M.D., Internal Medicine, Physiology. Assistant in Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

Bishop, David W., Ph.D., Physiology. Professor of Physiology, University of Massachusetts, Amherst, Mass.

Blivaiss, Ben B., Ph.D., Endocrinology. Instructor in Physiology and Pharmacology, The Chicago Medical School, Chicago, Ill.

Botts, Dorothy Jean, B.S., Physiology, Biophysics. Student, Research Assistant, University of Chicago, Chicago, Illinois.

Brownlee, Kenneth A., M.A., Biology. Department of Biometrics, E. R. Squibb & Sons, New Brunswick, N. J.

Buggs, C. W., Ph.D., Zoology, Bacteriology. Associate Professor of Bacteriology, Wayne University, Detroit, Michigan.

Bunkin, Irving A., M.D., Gynecology, Obstetrics. Adjunct Gynecologist and Obstetrician, Beth Israel Hospital, New York, N. Y.

Cohen, Monroe, M.D., Medicine. Physician, Private Practice, Brooklyn, N. Y.

Conn, Jerome W., M.D., Metabolism, Endocrinology. Associate Professor of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

Cook, Elton S., Ph.D., Biochemistry. Dean of Research, Institutum Divi Thomae, Cincinnati, Ohio.

Cook, Leonard, B.A., Pharmacology. Graduate Student in Pharmacology, Yale University, New Haven, Conn.

Dann, Sidney, M.D., Cardiology. Fellow, Department of Therapeutics, New York University College of Medicine, New York, N. Y.

Delson, Barnet, M.D., Obstetrics, Gynecology. Clinical Assistant, Brooklyn Cancer Institute, Brooklyn, New York.

Demsker, Robert C., B.A., Chemistry. Chief Chemist, Macy's Bureau of Standards, New York, N. Y.

Dembowski, Jan, Ph.D., Protozoology, Psychology. Director, The Nencki Institute for Experimental Biology, Lodz, Poland.

Di Caprio, Joseph M., M.D., Bacteriology. Assistant Resident in Internal Medicine, Long Island College Hospital, Brooklyn, N. Y.

Ekman, Birger, M.D., Cancer Vitamins. Visiting Associate, Sloan-Kettering Institute, New York, N. Y.

Ellison, Solon A., D.D.S., Bacteriology. Fellow in Bacteriology, Columbia University, New York, N. Y.

Glassman, Harold, Ph.D., Biochemistry. Biochemist, Biological Department, Camp Detrick, Frederick, Maryland.

Germuth, Frederick G. Jr., M.D., Immunochemistry, Pathology. Senior Assistant Surgeon, National Institute of Health, Silver Spring, Maryland.

Goodman, Laurence W., D.V.M., Veterinary Medicine. Practising Veterinarian, Manhasset, N. Y.

Gordon, Robert S., A.B., Medicine. Medical Student, Harvard Medical School, Boston, Mass.

Gots, Joseph S., Ph.D., Medical Bacteriology. Instructor, Department of Bacteriology, University of Pennsylvania Medical School, Philadelphia, Pa.

Greenwood, M. Allen, M.D., Medicine. Physician, Ophthalmologist, New York, N. Y.

Hamwi, George J., M.D., Endocrinology. Fellow in Medicine, Cornell University Medical School, New York, N. Y.

Jackson, John, D.V.M., Veterinary Medicine. Practicing Veterinarian, New York, N. Y.

Johnson, David H., M.S., Histology, Tissue Culture. Graduate Student, New York, N. Y.

Kahn, Robert L., M.S., Physiology. Instructor in Biology, Brooklyn College, Brooklyn, New York.

Karandikar, Gopal K., M.S., Pharmacology. Graduate Student, Yale School of Medicine, New Haven, Conn.

Kennedy, George H., A.B., Biometrics. Research Chemist, Biological Laboratory, E. I. Dupont de Nemours & Co., New Brunswick, N. J.

Kern, Fred Jr., M.D., Internal Medicine. Research Fellow in Medicine, Cornell University Medical School, New York, N. Y.

Kintish, Irving L., B.S., Biochemistry. Research Chemist, Bronx, N. Y.

Kozam, George, M.S., Peripheral Circulation, Hemorrhage. Instructor in Anatomy, New York University College of Dentistry, New York, N. Y.

Kraft, Irene, D.V.M., Veterinary Medicine. Owner of Dog & Cat Hospital, White Plains, N. Y.

Kuhl, Walter J. Jr., M.D., Internal Medicine. Assistant Resident, Medical Division, Bellevue Hospital, New York, N. Y.

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Levy, Marion J. Jr., Ph.D., Sociology. Assistant Professor of Sociology, Princeton University, Princeton, N. J.

Longacre, Dorothy Janet, M.S., Bacterial Nutrition. Microbiologist, National Dairy Research Laboratories, Inc., Oakdale, L. I., N. Y.

Lucatorto, Frank M., B.S., Indocrinology, Embryology. Graduate Assistant, De Paul University, Chicago, Illinois.

Machado, Paulo de Almeida, M.D., Antibiotics. Laboratories Manager, Johnson & Johnson do Brasil, Sao Paulo, Brazil.

Mark, Herbert, M.D., Internal Medicine. Assistant Resident, Medical Service, Montefiore Hospital, New York, N. Y.

Merrill, Byrd F., M.D., Internal Medicine. Resident in Internal Medicine, Long Island College Hospital, Brooklyn, N. Y.

Misler, Samuel, Nutrition, Biology. Research Assistant, National Dairy Research Laboratories, Oakdale, L. I., N. Y.

Moses, Campbell, M.D., Physiology, Internal Medicine. Assistant Professor of Medicine, Director, Addison H. Gibson Laboratory, University of Pittsburgh, Pittsburgh, Pa.

Muller, Julius F., Ph.D., Food Technology, Nutrition. Director of Research, Prescription Products Division, The Borden Company, New York, N. Y.

Murphy, Eugene F., Ph.D., Artificial Aids. Assistant Director for Research, Prosthetic & Sensory Aids Service, Veterans Administration, New York, N. Y.

Murphy, Rosemary A., M.D., Physiology, Internal Medicine. Staff Physician, Lahey Clinic, Boston, Mass.

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Parkinson, Martin C., B.S., Biochemistry. Biochemist in Cancer Research, Interchemical Corporation, Bronx, N. Y.

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Salisbury, Edward Irving, M.D., Tropical Medicine. Medical Director, United Fruit Company, New York, N. Y.

Scheuing, Lawrence Einor, B.S., Embryology. Graduate Assistant in Embryology, De Paul University, Chicago, Illinois.

Schneider, Paul, D.D.S., Dentistry. Chief Resident in Dentistry, Sea View Hospital, Staten Island, New York.

Schroeder, Conrad T. H., M.D., Medicine. Chief Resident in Medicine, Sea View Hospital, Staten Island, New York.

Sendroy, Julius Jr., Ph.D., Biochemistry. Chief Chemist, Naval Medical Research Institute, Bethesda, Maryland.

Simson, George A., M.D., Medicine. Fellow, Department of Therapeutics, New York University College of Medicine, New York, N. Y.

Slavin, Abraham, Sc.D., Department of Civil Engineering, Polytechnic Institute of Brooklyn. Consulting Civil Engineer and Architect, New York.

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Smith, Mary Frances Hayward, M.D., Gastroenterology. Senior Staff Member, Department of Gastroenterology, Lahey Clinic, Boston, Mass.

Smith, Richmond Watson Jr., M.D., Endocrinology, Metabolism. Research Fellow in Medicine, Cornell Medical College, New York, N. Y.

Spector, Aaron, Ph.D., Acoustics. Assistant Professor of Physics, Queens College, Flushing, New York.

Stern, Aaron, M.A., Psychology, Child Development. Research Assistant, New York University, New York, N. Y.

Straessle, Rudolf, Ph.D., Protein Chemistry, Biology, Chemistry, Physics. Research Fellow, Department of Physical Chemistry, Harvard Medical School, Boston, Mass.

Tafuri, John F., M.S., Entomology. Research Assistant, American Museum of Natural History, New York, N. Y.

Thomas, William C. Jr., M.D., Metabolism, Endocrinology. Instructor in Medicine, Cornell University Medical College, New York, N. Y.

Travell, Janet, M.D., Medicine, Pharmacology. Assistant Professor of Clinical Pharmacology, Cornell Medical College, New York, N. Y.

Warren, Sol L., Ph.D., Psychology. Supervisor of Vocational Rehabilitation, New York State Education Department, Brooklyn, New York.

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Yates, S. Blake, M.S., Chemistry, Medical Sciences. Patent Management, Research Corporation, New York, N. Y.

Yeomans, Andrew, M.D., Infectious Disease, Metabolic Disease. Chief, Medical Service, Veterans Hospital, White River Junction, Vt.

Zauder, Howard L., B.A., Pharmacology. Graduate Student, University of Vermont, College of Medicine, Burlington, Vt.

Zettlemoyer, Albert C., Ph.D., Physical Chemistry. Associate Professor of Chemistry, Lehigh University, Bethlehem, Pennsylvania.

STUDENT MEMBERSHIP

Abrams, Julian, M.S., Clinical Psychology. Student, New York University, New York, N. Y.

Fraser, Donald Alexander Stuart, M.A., Statistics. Student, Princeton University, Princeton, N. J.

Harvey, Francis J., M.D., Psychology, Biology. Interne, Coney Island Hospital, Brooklyn, N. Y.

Herman, Justin, B.A., Microbiology. Student, New York University, New York, N. Y.

Peisakoff, Melvin P., A.B., Mathematical Statistics. Graduate Student, Princeton University, Princeton, N. J.

Van Demark, Paul J., M.S., Bacteriology, Biochemistry. Standard Brands Fellow, Department of Bacteriology, Cornell University, Ithaca, N. Y.

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Warshaw, Sigmund S., M.A., Psychology. Ph.D. Candidate, New York University, New York, N. Y.